CLINICAL TRIAL PROTOCOL

Document Number:		**c03608483-05**
BI Trial No.:	1245.100	
BI Investigational Product(s):	Empagliflozin	
Title:	A double-blind, placebo controlled, cross-over renal mechanistic trial to assess the effect of adding empagliflozin versus placebo on renal hyperfiltration on a background of the angiotensin converting enzyme inhibitor (ACEi) ramipril: BETWEEN Study	
Brief Title:	Empagliflozin and ACEi– effects on hyperfiltration: BETWEEN Study	
Clinical Phase:	II	
Trial Clinical Monitor:	Phone: Fax:	
Principal Investigator:	Phone: Fax:	
Status:	Final Protocol (based on Global Amendment 3)	
Version and Date:	**Version: 4.0**	**Date: 03 Jul 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:			
Name of active ingredient:		empagliflozin	
Protocol date: 15 Sep 2015	**Trial number:** 1245.100		**Revision date:** 03 Jul 2018
Title of trial:	A double-blind, placebo controlled, cross-over renal mechanistic trial to assess the effect of adding empagliflozin versus placebo on renal hyperfiltration on a background of the angiotensin converting enzyme inhibitor (ACEi) ramipril: BETWEEN Study		
Principal Investigator	Phone: Fax:		
Trial site(s):			
Clinical phase:	II		
Objective(s):	The main objective of the study is to assess the effect of empagliflozin versus matching placebo when added to ramipril on reducing glomerular hyperfiltration (glomerular filtration rate (GFR) ≥ 135 ml/min/1.73m^2) under euglycaemic conditions.		
Methodology:	Randomised, double blind, double-dummy, placebo controlled, cross-over exploratory renal mechanistic study with empagliflozin compared to placebo added to open label ramipril. The analysis will be based on different GFR sub-groups. Patients will be classified as a hyperfilterer (GFR ≥ 135 mL/min/1.73m^2) or normofilterer (GFR <135 mL/min/1.73m^2) based on their screening GFR. After patients receive ramipril treatment, patients will be categorized as a responder (GFR < 135 mL/min/1.73m^2) or non-responder (GFR ≥ 135 mL/min/1.73m^2).		
No. of patients: **total entered:**	Approximately 74 randomised patients		
each treatment:	Approximately 37 patients in Sequence A: period 1 dosing with 25 mg empagliflozin added to open-label ramipril*and period 2 dosing with		

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	matching placebo to 25mg empagliflozin added to open-label ramipril*. Approximately 37 patients in Sequence B: period 1 dosing with matching placebo to 25 mg empagliflozin added to open-label ramipril* and period 2 dosing with 25 mg empagliflozin added to open label ramipril*. Patients will undergo a 4 week wash-out period (empagliflozin or matching placebo) between period 1 and period 2 dosing while remaining on a background of open-label ramipril*. *Background ramipril treatment: Patients will be dose escalated to 10 mg ramipril or to their maximum tolerated dose.
Diagnosis :	Type 1 diabetes mellitus (T1D), Type 2 diabetes (T2D), or obesity
Main criteria for inclusion:	Male or female patients at least 18 years of age, diagnosed with T1D, T2D or obesity at least 6 months prior to screening, with an HbA_{1c} between 6.5 to 11%, eGFR ≥ 60 mL/min/1.73m^2 and stable glycaemic status.
Test product(s):	empagliflozin
dose:	25 mg, once daily
mode of administration:	oral
Comparator products:	Matching placebo to 25 mg empagliflozin
dose:	NA
mode of administration:	oral
Background products:	ramipril
dose:	1.25 mg, 5 mg or 10 mg
mode of administration:	Oral
Duration of treatment:	Up to 5 week screening period 4 week run-in period: 1 week on 5 mg ramipril followed by 3 weeks on 10 mg ramipril 4 week Period 1 dosing 4 week wash-out 4 week Period 2 dosing
Endpoints	The primary endpoint is GFR under euglycaemic conditions after 4 weeks of treatment with either empagliflozin added to ramipril or placebo added to ramipril. Secondary endpoint

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	Filtration status (GFR < 120 mL/min/1.73m2; yes/no) after 4 weeks of treatment with either empagliflozin added to ramipril or placebo added to ramipril
Safety criteria:	Further safety endpoints include: Incidence of adverse events (AEs) Changes from baseline in clinical laboratory values
Statistical methods:	Restricted Maximum Likelihood Estimation based Mixed-effects Model for Repeated Measures analysis will be used to obtain adjusted means for the treatment effects. This model will include treatment and period as fixed effects, patient as a random effect and randomisation baseline (visit 8) as a covariate. Compound symmetry will be used as a covariance structure for within-patient variation. The primary analysis will be restricted to the subgroup of patients with GFR ≥ 135 mL/min/1.73m2 at screening (Visit 4). Other sub-groups will be analysed as secondary analyses. Binary endpoints will be analysed using McNemar's test.

FLOW CHART

Trial Period	**Screening**					**Run-in**				**Period 1 Dosing**			**Wash out**	**Period 2 Dosing**			**eEOT**	**Follow up**
Visit	**1**	**2**	**3**	**4**	**4a**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		**16**
Study Week	-9	-7	-7	-6	-4	-3	-1	-1	-1	3	4	4	8	11	12	12	**Early**	13
Study Day	-63	-49	-43	-42	-28	-21	-7	-2	-1	21	27	28	56	77	83	84	**Discn. only**	91
Preferred time window for visits (days)	-18 to -3	-3	NA	NA		+7	-3	NA	NA	±2	NA	NA	+7	±2	NA	NA	NA	+7
Clinic Visit	X		X	X	X	X		X	X		X	X	X		X	X	X	X
Phone Visit		X					X			X				X				
Fasting visit				X					X			X				X	X	X
Informed consent	X																	
Demographics	X																	
Medical history	X																	
Physical examination[1]	X															X	X	X
Vital signs[2]	X			X		X			X			X	X			X	X	X
Height	X																	
Weight and waist circumference[3]	X			X					X			X				X	X	
Laboratory tests[4]	X			X		X			X			X	X			X	X	X
Lipid panel and FPG				X					X			X				X	X	X
Ketone measurement at the site[5]			X	X				X	X		X	X	X		X	X	X	X
HbA_{1c}	X								X			X				X	X	X
Biomarker sample collection				X					X			X				X		
Pregnancy test[6]	X			X					X			X	X			X	X	
12 lead-ECG[7]	X																	X
Review in/exclusion criteria[20]	X				X				X									
Diet and exercise counselling[8]	Continuous																	
Home monitoring[9]	Continuous																	

Trial Period	**Screening**					**Run-in**				**Period 1 Dosing**			**Wash out**	**Period 2 Dosing**			**eEOT**	**Follow up**
Visit	**1**	**2**	**3**	**4**	**4a**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		**16**
Study Week	-9	-7	-7	-6	-4	-3	-1	-1	-1	3	4	4	8	11	12	12	**Early Discn. only**	13
Study Day	-63	-49	-43	-42	-28	-21	-7	-2	-1	21	27	28	56	77	83	84		91
Preferred time window for visits (days)	-18 to -3	-3	NA	NA		+7	-3	NA	NA	±2	NA	NA	+7	±2	NA	NA	NA	+7
Clinic Visit	X		X	X	X	X		X	X		X	X	X		X	X	X	X
Phone Visit		X					X			X				X				
Fasting visit				X					X			X				X	X	X
Modified diet[10]		X					X			X				X				
ABPM[11]			X					X			X				X			
24 hour urine collection[12]			X					X			X				X			
Dispense lithium tablet[13]			X					X			X				X			
Clamped euglycaemia including assessment of GFR[14]				X					X			X				X		
SNS / arterial stiffness / non-invasive cardiac output monitoring				X					X			X				X		
Renal panel[15]				X					X			X				X		
Dispense ramipril[16]					X	X			X			X	X					
Administer IMP(s)[17]					X	X		X	X		X	X	X		X	X		
Randomisation									X									
Dispense empagliflozin/ placebo[18]									X				X					
Phone Calls[19]				X		X			X			X	X			X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance check						X			X			X	X			X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Trial Period	**Screening**					**Run-in**				**Period 1 Dosing**			**Wash out**	**Period 2 Dosing**			**eEOT**	**Follow up**
Visit	**1**	**2**	**3**	**4**	**4a**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		**16**
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Preferred time window for visits (days)	-18 to -3	-3	NA	NA		+7	-3	NA	NA	±2	NA	NA	+7	±2	NA	NA	NA	+7
Clinic Visit	X		X	X	X	X		X	X		X	X	X		X	X	X	X
Phone Visit		X					X			X				X				
Fasting visit				X					X			X				X	X	X
Wash-out of existing RAAS therapy[21]	X																	
Trial termination																		X

1. Screening visit physical examination may be done any time during the screening period prior to the start of ramipril treatment.
2. At visit 1, BP should be measured in both arms. If BP differs by more than 10 mmHg, the arm with the higher BP should be used for subsequent measurements. For routine clinic visits, systolic and diastolic BP as well as pulse rate should be measured 3 times after 5 minutes of rest in the supine position. During renal study visits (visit 4, 8, 11 and 15); BP and pulse will be measured 3 times in the supine position (refer to Section 5.2.4).
3. Weight and waist circumference to be taken in the morning (refer to Section 5.2.5)
4. Routine safety labs include haematology, chemistry and routine urinalysis (A & B) including the local dipstick test for leukocyte and/or nitrite. C-peptide, TSH, urine albumin and creatinine will be measured at visit 1 (refer to Table 5.3.3:1).
5. In patients with T1D or patients who are only using insulin for management of diabetes, ketones should be measured at the site using the home monitoring device either immediately before or after the collection of laboratory samples. Ketones can be measured in a fasted or non-fasted state.
6. A pregnancy test will be performed in all women of child bearing potential. More frequent testing can be done if required per Investigator judgment.

7. Additional Electrocardiograms (ECGs) should be performed in cases of cardiac symptoms per Investigator judgment.
8. Patients will be advised to follow a healthy diet and exercise program based on Investigator recommendation during the study; during the 7 days preceding the start of the renal physiology laboratory assessments patients will be required to follow a modified diet (refer to Section 4.2.2.2).
9. Self-Blood Glucose Monitoring (SBGM) should be performed daily in patients with diabetes. Measurements should be taken, at least before breakfast, lunch, dinner and bedtime in patients with T1D and at least once per day or as directed by the investigator, in patients with type 2 diabetes (T2D). Obese patients (without diabetes) are not required to monitor blood sugars unless deemed necessary by the investigator. Additional measurements may also be warranted as per the usual care of patients. For further details see Section 5.3.2.1. Ketone measurements should be performed by the patient with T1D daily during the screening and treatment periods (excluding run-in and wash-out) and for 5 days after the end of double blind treatment. In case of any symptoms of diabetic ketoacidosis (DKA), more frequent monitoring may be required. Other conditions may also trigger the need for ketone measurement. Patients with T2D and obesity may measure ketones as per Investigator judgment. For further details see Section 5.3.2.2. Home blood pressure monitoring should be performed daily after starting ramipril. For further details see Section 5.3.2.3.
10. Patient will be instructed to adhere to a sodium enriched (preferably > 140 mmol/day) and moderate-protein (<1.5g/kg/day) diet during the 7 days preceding the start of renal assessments during screening, open-label treatment and double-blind treatment periods (the diet to continue until the end of renal assessments). Instruction for this diet will be included in the patient diary and reinforced by the site via a phone call. If a patient fails to adhere to the prescribed sodium enriched and moderate-protein diet, the Investigator will assess whether the patient is still eligible to start the renal assessments based on the patient's actual diet during the 7 days preceding the renal physiological assessments. In cases of an unsatisfactory diet, patients may have to be screen failed based on the Investigator's judgment.
11. The ambulatory blood pressure monitor (ABPM) device is initiated on the mornings of the specified visits before study medication intake, if applicable. Patient should return to the clinic on the following day to have the device removed after 24 hours of monitoring has been completed.
12. The 24 hour urine collection should start ideally one day prior to the renal visits (Visits 4, 8, 11 or 15) after the patient has been on the modified diet. Collected urine should be returned to the clinic on the following day.
13. Patients will be required to take a lithium tablet approximately 12 hours prior to Visit 4, 8 11 and 15 for the determination of segmental tubular sodium handling.

14. Assessments to be performed under euglycaemic conditions (glycaemia maintained between 4-6 mmol/L). Based on the glycaemic status of obese patients, a euglycaemic clamp may not be required based on Investigator judgment. In the event that a patient does not require a euglycaemic clamp, patients will still arrive at the study center in the morning (between 7:45 and 8:30 am) and will commence the inulin or iohexol and PAH infusion at approximately noon.

Time	Assessments – Inulin Procedure
07:45 – 8:30	Admittance to laboratory and preparation for clamp procedures to maintain desired glycaemia (4-6 mmol/l) throughout assessments for that day. Investigator to assess if a glycaemic clamp is required for non-diabetic patients.
11:30 – 11:55	Blood and urine samples collected for BHB analysis (to be collected within 30 min of starting the inulin and PAH infusion).
12:00	Start Inulin and PAH infusion. Study medication(s) to be administered in clinic during open label and double blind treatment periods. Neurohormone levels (RAAS mediators, NO), arterial stiffness, NICOM, markers of sympathetic nervous system activation (heart rate variability) and other laboratory assessments including renal panel samples will be obtained.
13:30-14:00	Continued Inulin and PAH infusion, assessment of MAP and clearance measurements (GFR, ERPF, FF, RBF, RVR) each based on the average of 2 measurements.
14:00	Continued Inulin and PAH infusion, assessment of MAP and clearance measurements (GFR, ERPF, FF, RBF, RVR) each based on the average of 2 measurements. Blood and urine samples collected for BHB analysis will be collected approximately 2 hours after the administration of study medication.

Time	Assessments – Iohexol Procedure
07:45 – 8:30	Admittance to laboratory and preparation for clamp procedures to maintain desired glycaemia (4-6 mmol/l) throughout assessments for that day. Investigator to assess if a glycaemic clamp is required for non-diabetic patients.
11:30 – 11:55	Blood and urine samples collected for BHB analysis (to be collected within 30 min of starting the ioxhexol bolus). Iohexol pre-dose sample to be collected.
12:00	Administer iohexol bolus infusion. Study medication(s) to be administered in clinic during open label and double blind treatment periods. Neurohormone levels (RAAS mediators, NO), arterial stiffness, NICOM, markers of sympathetic nervous system activation (heart rate variability) and other laboratory assessments including renal panel samples will be obtained.
14:00	Assessment of MAP and clearance measurements (GFR, ERPF, FF, RBF, RVR) each based on the average of 2 measurements. Blood sample collection for measurement of plasma iohexol, haematocrit and pre-dose PAH. Blood and urine samples collected for BHB analysis will be collected approximately 2 hours after the administration of study medication. Administer bolus of PAH.
14:30	Blood sample collection for measurement of plasma iohexol, haematocrit
15:00	Blood sample collection for measurement of plasma iohexol, haematocrit
15:30	Blood sample collection for measurement of plasma iohexol, haematocrit and PAH

16:00	Blood sample collection for measurement of plasma iohexol, haematocrit and PAH

15. The renal panel (refer to Table 5.3.3:2) and urinalysis C (refer to Table 5.3.3:1) will be performed at visits 4, 8, 11 and 15.
16. Site staff will dispense ramipril (5 mg) at visit 4a. Starting at visit 5, patient should be up titrated to 10 mg ramipril. A lower dose of ramipril (e.g. as low as 1.25 mg quaque die (once a day) (q.d.) may be administered based Investigator's discretion to alleviate potential side effects (e.g., hypotension) (refer to Section 4.1.3).
17. Ramipril study medication to be administered in the clinic during visits 4a, 5, 7 and 8 by delegated study staff. Ramipril and empagliflozin/placebo to be administered in the clinic during visits 10, 11, 14 and 15 by delegated study staff. At visit 12, only ramipril will be administered during the clinic visit.
18. At visit 8 and visit 12, site staff will dispense empagliflozin/placebo (but not administer) and instruct patient to start taking the empagliflozin/placebo medication starting the following morning (i.e. day 1 or day 57).
19. Site staff must contact the patient via phone daily for approximately 5 days following the start or dose adjustment of ramipril and start or stoppage of empagliflozin/placebo to reinforce compliance (if required), learn of any AEs or determine if the patient's insulin should be titrated.
20. Prior to visit 4a, site staff must review the GFR value obtained from visit 4 and determine if the patient would be eligible to enter run-in (visit 4a) in accordance with the recruitment caps outlined in Section 3.3.
21. If a patient is taking a RAAS inhibitor and may safely discontinue, in the opinion of the investigator, patients may commence a wash-out of their prescribed RAAS inhibitor after signing the informed consent form. Refer to Section 6.2.1 for further details.

TABLE OF CONTENTS

ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitor
ACEi	Angiotensin Converting Enzyme inhibitor
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIx	Augmentation Index
AP	Alkaline Phosphatase
ARB	Angiotensin II Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area under the curve
BHB	Beta-hydroxybutyrate
BP	Blood Pressure
cAMP	Cyclic adenosine monophosphate
CEC	Clinical Events Committee
cGMP	Cyclic guanosine monophosphate
CI	Confidence Interval
CKD	Chronic Kidney Disease
C_{max}	Maximum concentration
CRA	Clinical Research Associate
CSII	Continuous Sub-Cutaneous Insulin Infusion
DEDP	Drug exposure during pregnancy
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ERPF	Effective Renal Plasma Flow
ESRD	End Stage Renal Disease
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HbA_{1c}	Glycosylated Haemoglobin
HDL	High Density Lipoprotein
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LDL	Low-Density Lipoprotein
MDI	Multiple Daily Injections
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
NICOM	Non-Invasive Cardiac Output Monitoring

PAH	Paraaminohippurate
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PPS	Per-Protocol Set
q.d.	quaque die (once a day)
RAAS	Renin Angiotensin Aldosterone System
RBF	Renal Blood Flow
REML	Restricted Maximum Likelihood Estimation
REP	Residual Effect Period
RIS	Run-In Set
SAE	Serious Adverse Event
SBGM	Self-Blood Glucose Monitoring
SGLT-2	Sodium dependent Glucose co-Transporter - 2
SNS	Sympathetic Nervous System
SUSAR	Serious Unexpected Suspected Adverse Reaction
T1D	Type 1 Diabetes
TGF	Tubuloglomerular feedback
TS	Treated Set
TSH	Thyroid Stimulating Hormone
UGE	Urinary Glucose Excretion
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WBC	White Blood Cell

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Controlling blood glucose in diabetes patients leads to improved patient outcomes [R04-2186, R12-1489, R04-2173]. Unfortunately despite advances in oral anti-diabetic therapies, insulin formulation and delivery and refinement of pharmacokinetic (PK) properties of rapid- and long-acting insulin analogues, current therapy for patients requiring pharmacotherapy often does not lead to satisfactory glycaemic control. In fact, only a minor portion of patients achieve normalization of glycosylated haemoglobin (HbA_{1c}) and restoration of euglycaemia. Hence with the currently available treatment options, patients with diabetes often fail to maintain adequate blood glucose control. This not only leads to serious acute conditions such as severe hypoglycaemia and ketoacidosis but also may lead to debilitating secondary complications including heart disease, blindness and kidney failure [R10-6369]. Diabetic nephropathy is the most significant cause of renal failure in North America, accounting for >40% of cases. In addition to diabetes, there are other conditions, such as obesity, that increases the risk for the development of chronic kidney disease (CKD), including progression to end stage renal disease (ESRD) [R18-1327]. The rate of progression from CKD to ESRD is also increased in patients with elevated BMI, including those with class II obesity and above. The initial stages of renal disease are characterised by renal haemodynamic alterations that result in increased intraglomerular pressure and glomerular hyperfiltration. The pathogenesis of hyperfiltration is complex and involves changes in both neurohormonal/vascular factors (the vascular hypothesis) as well as tubuloglomerular feedback mechanism (TGF; the tubular hypothesis).

According to the vascular hypothesis for nephropathy, activation of the neurohormonal pathways such as the renin-angiotensin-aldosterone-system (RAAS) promotes renal injury in obese patients as well as in patients with diabetes [R10-6368, R96-3187, R18-1328, R18-1329]. RAAS activation results in persistent vasoconstriction of the efferent arteriole of the glomerulus which causes high intraglomerular pressure and renal hyperfiltration (GFR ≥ 135 ml/min/1.73m^2), which is a risk factor for progressive nephropathy and early blood pressure (BP) abnormalities [R10-6368, R96-3187]. Current standard therapy against proteinuria and early nephropathy therefore includes the blockade of RAAS [R96-3190, R02-0327]. Unfortunately ACEi and angiotensin II receptor blockers (ARBs) incompletely suppress the RAAS. As a consequence of the incomplete physiological effect on hyperfiltration, RAAS inhibitors have failed clinically as a preventative therapy in diabetes as they do not completely eliminate renal or cardiovascular complications. Unfortunately > 25% of T1D patients will develop diabetic nephropathy despite RAAS blockade and this risk is increased in patients with hyperfiltration [R10-6368, R96-3190]. Similarly in obese patients, long term reduction in proteinuria induced by RAAS blockade appears to be exhausted over time, particularly in absence of weight loss or if there is further weight gain [R18-1330].

The tubular hypothesis is based on an increase in proximal tubular glucose delivery that is due to chronic hyperglycemia in diabetes. This leads to a maladaptive increase in glucose reabsorption along with sodium via the Sodium dependent Glucose co-Transporter - 2 (SGLT-2) in the proximal tubule [P13-16965]. As a result, distal sodium chloride delivery to the macula densa is decreased which is sensed as a reduction in effective circulating volume

by the juxtaglomerular apparatus causing an afferent renal vasodilatory response. The consequence of this altered TGF results in hyperfiltration and increased intraglomerular pressure [R12-5147].

It was demonstrated nearly four decades ago, that in patients with poorly controlled T1D, the maximum tubular reabsorption capacity for glucose was significantly increased, whereas one would 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 T1D could be explained by an up-regulation of glucose transporters, including SGLT-2, which was demonstrated in tubular cells cultured from patients with T2D [R10-0703]. The phenomenon of increased glucose reabsorption when glucose concentration is elevated could therefore be considered a maladapted response to glycosuria in diabetes, since it would rather be desirable for the kidney to excrete the filtered glucose load in order to restore normoglycaemia [P11-10364]. In the EMPA-REG Outcome Study, inhibition of SGLT2 by empagliflozin, is associated with slower progression of kidney disease and lower rates of clinically relevant renal events compared with placebo as add-on to standard of care therapy for T2D [P16-06807].

In animals and in humans, inhibition of SGLT-2 reduces renal hyperfiltration by a magnitude that is similar to ACEi suggesting a protective decline in intraglomerular pressure [R10-6368, P13-16965]. The effect of 8 weeks of treatment with empagliflozin has been studied in hyperfiltering patients with T1D [P13-16965]. In this patient population, treatment with 25 mg empagliflozin reduced renal hyperfiltration by – 33 ml/min/1.73m^2 to 139 ± 25 ml/min/1.73m^2 which was statistically significant compared with normofilterer patients. The magnitude of the SGLT-2i effect on hyperfiltration was similar to that achieved with an ACEi. However neither agent alone could abolish renal hyperfiltration [P13-16965].

Based on the pathophysiological considerations, use of RAAS inhibition combined with SGLT-2i may suppress both the neurohormonal (RAAS) and tubular (SGLT-2) pathways that are central to the pathogenesis of early nephropathy.

1.2 DRUG PROFILE

Empagliflozin is a novel, orally available, potent and selective inhibitor of renal SGLT-2. SGLT-2 is a member of a larger group of sodium substrate co-transports, the sodium-glucose co-transporter 5 gene family [R05-0939]. Under normoglycemia, glucose is completely reabsorbed by SGLTs in the kidney, whereas the re-uptake capacity of the kidney is saturated at plasma glucose concentrations higher than approximately 10-11 mmol/L, resulting in glycosuria. This threshold concentration can be decreased by SGLT-2 inhibition [c01678844-07] with a selectivity approximately 5000-fold over human SGLT-1 (IC_{50} 6278 nM), responsible for glucose re-absorption in the gut, was calculated for empagliflozin [c01678844-07]. Selective inhibition of SGLT-2 reduces renal reabsorption of glucose and promotes increased urinary glucose excretion (UGE) resulting in reduction of blood glucose levels.

Empagliflozin has been developed for treatment of Type 2 diabetes (T2D) mellitus and has received marketing approval in various regions including the European Union, Canada 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 [c01678844-07].

1.2.2 Clinical pharmacokinetics

1.2.2.1 Clinical pharmacokinetics – Type 2 diabetes mellitus

In healthy volunteers and in patients with T2D, 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 clinical meaningful. The observations from a Phase I study in patients with renal impairment and end-stage renal disease indicate a low 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 antidiabetic medications, warfarin, verapamil, ramipril, simvastatin, digoxin, hydrochlorthiazide, torasemide, gemfibrozil, rifampicin, probenecid and oral contraceptives (Microgynon®).

For further details refer to the current version of the IB for empagliflozin [c01678844-07].

1.2.2.2 Clinical pharmacokinetics – Type 1 diabetes mellitus

To support the development of empagliflozin for the T1D indication, a PK/PD (pharmacodynamics) study with a 4 week treatment duration has been completed (Trial 1245.78 – EASE-1), [c02435449-01]. Empagliflozin daily doses of 2.5 mg, 10 mg and 25 mg were evaluated in this trial.

Empagliflozin was rapidly absorbed after oral dosing with median t_{max} around 1.5 hours for all empagliflozin dose groups. Dose-normalised AUC (area-under-the-curve) and C_{max} were similar for all doses after a single dose and at steady-state, demonstrating a dose-proportional increase in empagliflozin plasma exposure. The accumulation ratio (AUC) ranged from 1.04 to 1.2, indicating limited accumulation of empagliflozin in plasma at steady-state. Terminal half-life was 12 to 16 hours after multiple doses. The inter-subject variability was low for but AUC and C_{max}, with a gCV% between 21.8% and 31.3%. The cumulative amount of empagliflozin excreted in urine was comparable on both Days 1 and 28 of treatment, with 15% to 20% of the dose excreted in urine across the 2.5 mg to 25 mg dose range.

1.2.2.3 Clinical pharmacokinetics and pharmacodynamics – comparison in Type 1 vs Type 2 diabetes mellitus

Empagliflozin PK/PD has been compared in patients with T1D versus T2D. Two 4 weeks trials were used: trial 1245.78 (EASE-1) in patients with T1D using empagliflozin daily doses of 2.5 mg, 10 mg and 25 mg, and trial 1245.4 in patients with T2D evaluating empagliflozin 10 mg, 25 mg and 100 mg.

In both patient populations, empagliflozin was rapidly absorbed reaching peak levels in approximately 1.5 hours post-dose. Thereafter, plasma levels declined in a biphasic fashion. There were no clinically relevant differences in empagliflozin exposure (AUC and C_{max}) between the two populations and the terminal elimination half-life appeared to be similar. Renal clearance and fraction of empagliflozin excreted in urine were also similar. Empagliflozin exposure increased in a dose proportional manner over the dose range tested in both studies.

In both patient populations, oral administration of empagliflozin results in increased UGE at all dose levels. Following a 4 week treatment, increases in UGE from baseline were approximately 78 g, 103.1 g and 101.5 g with 2.5 mg, 10 mg and 25 mg empagliflozin once daily, respectively, in patients in T1D and 64.4 g, 78.4 g and 72.6 g with 10 mg, 25 mg, and 100 mg empagliflozin once daily, respectively in patients with T2D. Results indicate that increases in UGE reached a plateau with empagliflozin 10 mg once daily in both populations. In addition, preliminary exposure – response analysis showed that approximately 56%, 77%, 87% and 95% of maximal effect on UGE was achieved with 2.5 mg, 5 mg, 10 mg and 25 mg empagliflozin once daily, respectively, indicating that near maximal effects on UGE in patients with T1D were observed with empagliflozin 10 mg and 25 mg once daily.

Overall, there were no clinically relevant differences in PK/PD of empagliflozin in patients with T1D compared with T2D. Empagliflozin PK was similar between the two populations and drug exposure increased in a dose proportional manner over the dose range evaluated. Increased UGE was observed following oral administration of empagliflozin at all dose levels and appeared to reach a plateau at empagliflozin 10 mg once daily in both populations [c02435449-01].

1.2.3 Clinical efficacy and safety

1.2.3.1 Clinical efficacy and safety – type 2 diabetes

Approximately 550 healthy volunteers were exposed to empagliflozin (up to 800 mg single dose and up to 50 mg qd). In addition, approximately 250 patients with T2D included in phase I trials received multiple dosing with empagliflozin up to 100 mg. Overall approximately 6900 patients with T2D have been treated with empagliflozin for at least 24 weeks. Of those patients, approximately 4900 patients have been treated for 52 weeks and approximately 2800 patients have been treated for at least 76 weeks.

The phase III studies have shown that treatment of 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 SBP up to 4.8 mmHg compared to placebo. This was consistently observed with empagliflozin as monotherapy, add on to metformin, to metformin + sulphonylurea, to pioglitazone with or without metformin, and to basal insulin with metformin and/or sulphonylurea. Phase III studies up to 104 weeks in T2D support the sustained effect of empagliflozin.

In clinical studies, empagliflozin was well tolerated in both normal healthy volunteers and patients with T2D up to maximal treatment duration of 104 weeks in completed studies. The frequency of overall adverse events (AEs), AEs leading to discontinuation and Serious Adverse Events (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 estimated Glomerular Filtration Rate (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 m^2) treatment with empagliflozin was well tolerated and lead to statistically significant reduction of HbA_{1c} and clinically meaningful improvements in fasting Plasma Glucose (FPG), body weight and BP compared to placebo at week 24. Similar results were sustained for up to 52 weeks [c01678844-07].

1.2.3.2 Clinical efficacy and safety – Type 1 diabetes mellitus

Two trials have been completed in patients with T1D. The first completed trial was Trial 1245.46 (ATRIMA), which assessed the impact of 8 weeks of treatment with once daily empagliflozin 25 mg on renal hyperfiltration [c01802271-02]. The second completed trial was Trial 1245.78 (EASE-1), a 4 week PK and PD trial, which assessed 3 doses of empagliflozin (2.5 mg, 10 mg and 25 mg) compared with placebo on 24-hour UGE and other glycaemic parameters after 7 days and 28 days [c02435449-01].

In 1245.46, which was an uncontrolled open-label pilot trial, empagliflozin taken for 8 weeks as adjunctive to insulin therapy was generally well-tolerated; 42 patients took empagliflozin and 40 successfully completed the study. Two patients prematurely discontinued from the trial due to DKA; one case occurred concurrently with gastroenteritis, and the other case followed insulin pump malfunction; both patients recovered from DKA. After 8 weeks of treatment in this trial, the mean change (SE) in GFR with empagliflozin 25 mg once daily in the hyperfilterer group was -33.4 (6.2) mL/min/1.73 m^2 from a baseline of 172.2 mL/min/1.73 m^2 under euglycaemia ($p<0.0001$) and -44.5 (7.1) mL/min/1.73 m^2 from a baseline of 186.4 mL/min/1.73 m^2 under hyperglycaemia ($p<0.0001$). In contrast, the mean GFR did not change significantly in non-hyperfilterer patients at the end of treatment. It was therefore concluded that short-term treatment with empagliflozin attenuated renal hyperfiltration in patients with T1D, possibly by affecting tubular-glomerular feedback mechanism.

Empagliflozin was also evaluated in this trial for its potential efficacy on glycaemia and rates of hypoglycaemia in patients with T1D as an adjunctive to insulin therapy. After 8 weeks of treatment with empagliflozin, a clinically significant mean (SE) increase in UGE of 114.6 (9.2) g/day was observed from a baseline value of 18.9 g/day. Based on the 40 patients who completed 8 weeks of empagliflozin treatment, the mean change (SE) in HbA_{1c} from baseline to end of treatment was -0.40 (0.08)% from a mean baseline HbA_{1c} (SD) of 8.03 (0.91)%. The mean change (SE) in FPG from a baseline mean (SD) of 10.01 (4.87) mmol/L was -1.39 (0.73) mmol/L. Symptomatic hypoglycaemia (defined by a blood glucose value of < 3.0 mmol/L based on Home Blood Glucose Monitoring) declined from a mean of 0.12 events per day in the 2 week placebo run-in period to 0.04 events per day in the last 2 weeks of the

treatment period. The mean change (SE) in total daily insulin dose at the end of treatment was approximately -8.9 (1.7) units/day from a baseline mean (SD) of approximately 54.7 (20.4) units/day primarily driven by a reduction in basal insulin. Decreased total insulin requirements were observed, despite patient-reported increased carbohydrate intake during the same periods; mean change (SE) of 53.78 (14.56) grams per day from a mean (SD) baseline value of 176.82 (121.09) grams/day.

These exploratory glycaemic results showed that the addition of empagliflozin 25 mg once daily to insulin in the treatment of T1D resulted in an HbA_{1c} reduction after 8 weeks, accompanied by a reduction in hypoglycaemic events, reduce insulin requirements and reduced glucose variability. The safety profile did not show any unexpected AE trends in the small population studied in this uncontrolled pilot trial [c01802271-02].

In trial 1245.78, a randomised, double-blind, placebo-controlled, parallel group trial, UGE increased from baseline to day 7 for all empagliflozin doses compared with placebo with a maximum UGE increase of around 100 g/24 hour in the empagliflozin 10 mg and 25 md dose groups. UGE values continued to increase until the end of the treatment period. In this study, 75 patients took empagliflozin or placebo and all of them successfully completed. Other relevant conclusions drawn from the study were as follows [c02435449-01]:

- An overall improvement was seen in glycaemic control with empagliflozin treatment compared with placebo. This was reflected by: (i) a reduction in HbA_{1c} compared with placebo for all 3 doses of empagliflozin from baseline to Day 28, with the greatest reduction (0.49%) observed in the empagliflozin 25 mg group; (ii) a reduction in the recorded total daily insulin dose of > 10% at week 4 with empagliflozin treatment compared with placebo.
- Treatment with empagliflozin over 28 days as adjunctive therapy to multiple daily injections (MDI) of insulin was well tolerated. More than 90% of patients were reported with hypoglycaemic events, of either mild or moderate intensity. No cases of DKA were reported; numerical increases in beta-hydroxybutyrate (BHB) values from baseline to last value on treatment were seen in all empagliflozin dose groups. After 4 weeks, following an insulin-adjustment period (day 8 to day 28), treatment with empagliflozin in patients with T1D resulted in a numerically lower frequency of patients symptomatic hypoglycaemia with plasma glucose < 54 mg/dL (< 3.0 mmol/L) compared with placebo without any hypoglycaemic episodes requiring assistance reported for empagliflozin.

In summary given the safety profile in the pre-clinical 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 T1D and T2D patients.

For further details please see the current version of the empagliflozin IB [c01678844-07] which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Patients with diabetes or obesity are at greater risk of developing nephropathy, potentially leading to end stage renal disease. The pathophysiology of these complications may be partially mediated by activation of the RAAS leading to renal haemodynamic abnormalities including efferent arteriolar vasoconstriction, an event which is postulated to result in renal hyperfiltration ultimately culminating in organ injury. Inhibition of the RAAS with an ACEi will reduce GFR in patients with diabetes and renal hyperfiltration and in non-diabetic obese patients but does not completely normalize the GFR under euglycemic conditions in all patients. Although patients with hyperfiltration may have an upregulated RAAS, other physiological factors are influencing the intraglomerular pressure and filtration rate.

During chronic hyperglycaemia, there is increased glucose and sodium re-absorption via SGLT-2 which results in decreased sodium delivery to the macula densa. This results in increased afferent renal vasodilation, increased intraglomerular pressure and renal hyperfiltration. Blockade of sodium reabsorption at the proximal tubule of the nephron via SGLT-2i reverses this effect and has been shown to reduce renal hyperfiltration [c01802271-02, P13-16965]. The magnitude of this effect, however, is similar to that of ACEi (i.e. around 33 ml/min/m^2) and does not completely normalize filtration rate.

This study is designed to determine if therapy with SGLT-2i (empagliflozin) added to ramipril (ramipril) will result in normalization of filtration rate. Since eGFR measurements are unreliable in providing accurate estimates of actual GFR, actual GFR will be measured using direct, measured clearance techniques under conditions of euglycaemia.

2.2 TRIAL OBJECTIVES

The main objective of the study is to assess the effect of empagliflozin versus matching placebo when added to ramipril on reducing glomerular hyperfiltration GFR ≥ 135 ml/min/1.73m^2) under euglycaemic conditions.

Other exploratory objectives of the study will investigate the effect of adding empagliflozin versus matching placebo when added to ramipril on:

- segmental tubular sodium (Na+) handling
- distal Na+ delivery and impact on afferent vasoconstrictors such as adenosine
- diurnal and nocturnal BP lowering based on ambulatory BP monitoring (ABPM) and,
- non-invasive determinants of cardiac output (see to Section 5.2.7), systemic vascular resistance and arterial stiffness.

2.3 BENEFIT - RISK ASSESSMENT

The overall safety and tolerability profile of empagliflozin is outlined in Section 1.2.3. Ramipril is approved for use in Canada and ACEi, including ramipril, are often used as first

line therapy to prevent the onset and progression of nephropathy in patients with diabetes. The current IB for empagliflozin supports chronic administration to patients with diabetes.

Inclusion of patients who do not have diabetes is also allowed in this trial. It has been shown that in healthy volunteers dosing with empagliflozin results in glycosuria summing up to about 2/3 the average glucosuria in patients with T2DM. This is similar to the amount of glucose lost in T2DM subjects with moderate renal impairment.

There are no long-term safety data for empagliflozin in patients without diabetes. Data in non-diabetic subjects is limited to healthy volunteers, without significant co-morbidities or concomitant medications. Exposure in healthy volunteers is from single dose and multiple dose studies with exposure up to 28 days. However, while limited, such data does include over 500 healthy volunteers exposed to empagliflozin during the clinical development for treatment of T2DM. No specific safety concern was identified and no occurrences of symptomatic hypoglycemia were detected [U12-2707-01]. It is noted that in patients with T2DM the risk of hypoglycemia was only increased with empagliflozin compared to the placebo group in patients who were concomitantly treated with insulin or a sulfonylurea. Further, in a mechanistic study [c11963611-01], subjects without DM were shown to increase endogenous glucose production in response to glucosuria after administration of empagliflozin. As a result, blood glucose levels remained in the normal range for these individuals [P16-01830]. Therefore, it is scientifically reasonable to hypothesize that in non-diabetic patients, with no medical indication for insulin or sulfonylurea treatment that the risk of hypoglycemia associated with empagliflozin treatment would be lower than in patients with T2DM.

Because the mode of action, blockade of the SGLT2 with consequent glucosuria, and natriuresis, is the same in patients with and without diabetes, although to different degrees, it is considered likely that the tolerability of empagliflozin is likely similar in patients without DM compared to patients with T2DM.

The Principal Investigator (PI) and team have extensive experience with the techniques required to conduct this study. The PI has conducted previous studies in patients with diabetes with ACEi as well as recently completed an 8 week proof-of-concept study that demonstrated that treatment with empagliflozin reduces renal hyperfiltration [c01802271-02].

In this trial, all patients will receive ramipril. Ramipril is generally well tolerated and has a well-defined safety profile. The initial starting dose will be 5 mg and patients will be up titrated to 10 mg after one week of treatment. All patients must meet the BP eligibility criteria at the start of the trial. During the course of the study, patients will receive a home BP monitor so that they can check their BP daily. In addition, patients will have their BP, renal function and electrolytes checked prior to initiating treatment and during treatment with ramipril. To mitigate the potential risk of hypotension, patients who are unable to tolerate the 10 mg q.d. may be dose reduced to a lower dose, with the lowest possible dose being 1.25 mg q.d. based on Investigator judgment. It is expected that some patients with hyperfiltration at screening may benefit from the ramipril treatment and their GFR may be reduced to < 135 mL/min/1.73m^2 whereas some patients may not respond to ramipril and their GFR will be ≥ 135 mL/min/1.73m^2 (hyperfilterer) after treatment with ramipril [R10-6368].

During the course of the study, all patients will receive empagliflozin during one of the two treatment periods. Although the treatment period is short, patients may receive short-term

benefit from the positive glycaemic and weight reduction effects of empagliflozin. In the 1245.78 trial (EASE-1), it was demonstrated that patients treated with empagliflozin had a 0.49% placebo-corrected decrease in HbA_{1c} compared to those patients on placebo after only 4 weeks of treatment ($p < 0.05$). In addition patients treated with empagliflozin had a > 10% reduction of the total daily insulin dose as well as weight loss after 4 weeks of treatment with empagliflozin treatment compared with placebo.

The rate of hypoglycaemia induced by insulin may not be aggravated by empagliflozin 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). Nonetheless, during the treatment periods, patients will be closely monitored for hypoglycaemic episodes through self-glucose monitoring (including overnight glucose monitoring) and through contact with the study staff, who will call the patients daily for approximately 5 days after the start or stoppage of blinded empagliflozin / placebo treatment or after ramipril dose adjustment. Patients will be educated on the signs and symptoms of hypoglycaemia as well as trained on the proper use of the self-glucose monitoring devices that will be provided through the trial.

This is a placebo-controlled trial and due to the cross over design, all patients will receive the empagliflozin matching placebo. During treatment with placebo, patients will not receive additional benefit, however the impact on their glycaemic control is considered to be minimal as all patients will continue to follow an appropriate Investigator-recommended diabetes treatment algorithm in order to achieve optimal and individualised glycaemic goals.

The combined effect of the ACEi and SGLT-2i is expected to reduce or potentially normalize hyperfiltration in patients with renal hyperfiltration. Although long term or sustained benefit from short term treatment is unlikely, the information gathered in this study would be proof-of-concept to further evaluate the potential renal benefits of empagliflozin in patients with diabetes in longer term studies and in larger patient populations.

Normofiltering patients (GFR = 90-134 ml/min/1.73m^2) will also be included in this trial. It is expected that renal haemodynamic function (and sodium handling) with ramipril versus empagliflozin added to a background of ramipril will remain largely unchanged in this group based on results from the ATIRMA trial (1245.46) [c01802271-02] and a study with RAAS inhibition with enalapril [R10-6368]. Inclusion of these patients will allow for direct comparisons between patients with renal normofiltration versus patients with renal hyperfiltration rather than referencing “historical” controls. Given that the potential risk to renal haemodynamic function and sodium handling is low and that patients with normofiltration will be carefully monitored throughout the study, some patients with normofiltration will be included in this trial.

In patients with diabetes, special attention will be paid to prevent DKA as outlined below. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA. Diabetic patients who are treated with insulin and receiving empagliflozin are 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 diabetic patients will be made aware of this risk and those diabetic patients utilizing insulin to manage their diabetes will be instructed not to reduce their insulin dose below Investigator

recommendations. In addition to frequent blood glucose monitoring, patients will measure ketones at least daily when treated with empagliflozin, including for 5 days after stopping the empagliflozin / placebo treatment. More frequent ketone monitoring will be performed in case of any symptoms of DKA, i.e. nausea, vomiting and abdominal pain. Patients will be instructed to do this irrespective of the glucose value in the event of DKA symptoms occurring. A ketone meter will be provided to the patient for this purpose. Patients will be taught how to interpret 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.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when ramipril or empagliflozin are administered. Angioedema has been reported in 0.1% of patients taking ramipril in clinical studies. Patients who have a history of angioedema would be excluded from participating in the study and any patient who experiences angioedema while on treatment should immediately stop taking ramipril.

Women who are of child-bearing potential will only be included in this study provided if they are using highly effective methods of contraception (c.f. Section 3.3.3). In the embryo-fetal and fertility studies in rats and rabbits, empagliflozin had no effects on early embryonic development, mating, male and female fertility, and only a moderate reversible effect on body weight of bearing live young were observed up to a dose of 300 mg/kg. However, use of ramipril during pregnancy and breastfeeding is contraindicated because ramipril can cause fetal and neonatal morbidity and mortality. These risks will be mitigated through ensuring that patients understand the requirement and will use highly effective methods of contraception throughout the conduct of the study. Pregnancy testing will be conducted on all women of child bearing potential during the study.

All patients may derive general medical benefit from the careful and close monitoring by medical personnel during the study. 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 in jeopardy.

Other risks to the patients are the risks inherent to any clinical trial such as unexpected adverse clinical event.

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

Given the favourable safety and tolerability profiles of both ramipril and empagliflozin, the careful monitoring of patients during the study and the ability to adjust the insulin requirements based on need, the sponsor considers the benefit-risk assessment of this trial to be favourable.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This double-blind, placebo-controlled, cross-over design exploratory study aims to evaluate the impact of adding empagliflozin or placebo to open label ramipril on GFR under euglycaemic conditions in patients with or without renal hyperfiltration. Randomisation to blinded treatment will not be stratified according to baseline GFR.

On specified study days, patients will be admitted to the renal physiology lab where their renal and systemic vascular functions will be assessed under controlled conditions of euglycaemia. Assessments will be conducted at screening (day -42), run-in (day -1) and study days 28 (period one dosing) and 84 (period two dosing). Patient participation is concluded when a patient has completed the last planned study visit. The end of the trial is defined as the "last patient out" (i.e. the last Visit 16 completed by the last patient in the trial). For a graphical representation of the trial, see Figure 3.1:1 below.

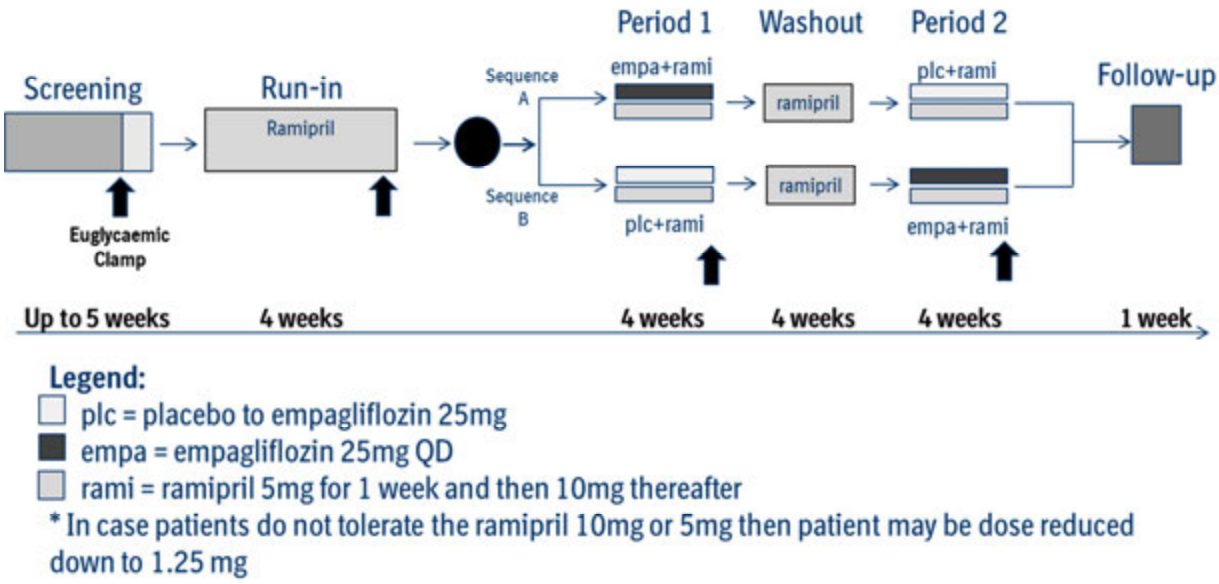


Figure 3.1:1 Trial Design

Please refer to Section 5.3.6 for assessment of AEs and Section 5.3.7 for AE collection and reporting.

3.1.1 Administrative structure of the trial

This trial is sponsored by Boehringer Ingelheim Canada Ltd.

Boehringer Ingelheim will appoint a Trial Clinical Monitor, responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial,

ensures appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

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

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

The organisation of the trial in Canada will be done by the local BI-organisation. A CML will be appointed responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs.

Documents on PI and other important participants, especially their curricula vitae, will be filed in the TMF document.

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

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in ISF.

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

3.1.1.1 Clinical Event Committee – severe hypoglycaemia, DKA

An independent external committee (Clinical Event Committee or 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 5.3.5.3). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, the study site 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.

3.1.1.2 Hepatic event adjudication

Certain hepatic events will be adjudicated/assessed 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 be defined by abnormal laboratory values and/or relevant AEs or both. For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested including laboratory values, hospital discharge letters, and medical reports from other physicians, if applicable. 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 a project level).

3.1.1.3 Clinical Event Committee – cardiovascular events

An independent external committee (Clinical Events 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, hospitalization 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, the study site will be asked to provide clinical documentation such as 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.

3.1.1.4 Data monitoring committee

A data-monitoring committee (DMC), independent of the Sponsor, will be established to assess the progress of the clinical trial, including an unblinded safety assessment at specified intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial. Measures are 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.

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

This is a mechanistic study where patients will receive open-label ramipril and then are randomised to either Sequence A (period 1 dosing with 25 mg empagliflozin and period 2 dosing with matching placebo to 25 mg empagliflozin) or Sequence B (period 1 dosing with matching placebo to 25 mg empagliflozin and period 2 dosing with 25 mg empagliflozin). Patients will undergo a 4 week wash-out period between period 1 and period 2 dosing. The trial is designed to assess the additive effect of empagliflozin added to RAAS inhibition on renal function under conditions of euglycaemia.

The cross-over design was selected since each patient will act as their own control and will therefore reduce the variability in the data. It is not expected that there will be significant sequence effect since, based on previous research, it is expected that the hemodynamic changes resulting from the treatments will occur rapidly and the 4 week wash-out period is long enough to ensure that any effects from the previous treatment sequence have diminished to baseline.

All eligible patients will be started on ramipril during a 4 week open-label run-in period. RAAS inhibition, including ACEi therapy, is the current standard of care to slow down the progression of diabetic kidney disease. Therefore ramipril therapy was selected as the background treatment in this study. Recommended starting dose is 5 mg q.d. ramipril with

titration up to 10 mg dose of ramipril after 1 week of treatment and will remain preferably on 10 mg ramipril for the remainder of the study.

Patients who are eligible to be randomised will be randomly assigned to either Sequence A or Sequence B in a blinded manner. It is expected that patients will continue to take 10 mg ramipril during both period 1 and period 2 dosing and throughout the 4 week wash-out that will separate each dosing period. It is expected that any changes to renal function would be seen after 4 weeks of randomised treatment.

Although all patients will be randomised to one of two treatment sequences, patients will be defined as either a hyperfilterer (GFR is ≥ 135 mL/min/1.73 m^2) or normofilterer (GFR is < 135 mL/min/1.73 m^2) based on their GFR during the screening period (visit 4). Additionally, patients will be categorised as either a responder to ramipril treatment (i.e., GFR is < 135 mL/min/1.73 m^2) or a non-responder to ramipril treatment (i.e., GFR is ≥ 135 mL/min/1.73 m^2) based on their GFR at the end of run-in (visit 8). The planned efficacy analysis will be conducted based on these sub-groups as it has been found in a previous study that the response to empagliflozin is strongly correlated with the baseline GFR measurement [c01802271-02]. Randomisation will not be stratified based on these sub-groups due to several reasons. Each randomized patient will receive empagliflozin treatment as well as the matching placebo and the order in which these treatments are administered is not expected to influence the GFR results due to the lengthy wash-out period. Given that a cross over design is employed and each patient will act as their own control, stratification of randomisation by GFR is deemed to be not necessary.

The follow-up period is 1 week, which is considered to be sufficient with empagliflozin have shown that the PD effect of empagliflozin only extends to about three days after the last dose [c01678844-07].

This trial includes a control group. The empagliflozin placebo control group is needed to control for what may be a small additive effect of empagliflozin when added onto ramipril treatment in reducing GFR. This control group will also provide control for the safety data that will be collected in this study. All patients will continue to take their insulin therapy, which can be adjusted per Investigator guidance throughout the conduct of the trial and therefore, optimized care will be maintained.

The trial contains a comparator group which will include normofiltering patients (GFR = 60-134 ml/min/1.73m^2). In this group of patients, it is expected that renal haemodynamic function (and sodium handling) with monotherapy (SGLT-2 or-ACE inhibition) or combination therapy with the 2 agents will remain largely unchanged. In contrast, it is expected that in the group with renal hyperfiltration significant effects on the renal haemodynamic parameters will be exhibited. Similarly, between group differences may be expected for BP and systemic vascular measures. As a result, it is important to include this control group so that it can be determined if the effects seen in patients with renal hyperfiltration are due to the neurohormonal and/or tubular hypothesis.

3.3 SELECTION OF TRIAL POPULATION

It is planned that approximately 150 patients will be screened to ensure the randomisation of approximately 74 patients. In order to adhere to the proposed sample size and ensure that an

adequate number of patients with hyperfiltration are entered, no more than 40 normofilterer patients (approximately 30 patients with T1D and approximately 10 patients who have T2D or are non-diabetic, obese individuals) will be entered based on GFR assessment at visit 4. As a result, screening for the study will continue until the required numbers of hyperfilterer patients based on GFR at visit 4, have been randomised to trial treatment.

Re-screening:

Re-screening of the same patient is allowed after discussion with sponsor. If a patient is re-screened, the patient should be declared a screening failure in the eCRF and IRT with their original patient number. Upon re-screening, the next available (i.e. new) patient number should be selected from electronic data capture (eDC) system. The patient must be re-consented using the current, approved version of the informed consent form.

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

This study will be performed in adult patients with obesity, T2D, or T1D, who are on insulin pump therapy (continuous subcutaneous insulin infusion or CSII) or MDI treatment. Patient eligibility will be assessed based upon a complete medical history including a physical examination and clinical laboratory tests.

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

3.3.2 Inclusion criteria

1. 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 patients diagnosed with T1D at least 6 months prior to informed consent or T2D or non-diabetic obese patients

3. T1D patients must use and be willing, based on the Investigator's judgement, to continue throughout the duration of the trial, either:

   - MDI's of insulin consisting of any type of subcutaneous insulin (and be willing to continue on MDI therapy during the course of the study) OR

   - CSII of any insulin type, with at least 3 months experience of using CSII prior to Visit 1

4. For patients with T1D or T2D, HbA_{1c} of 6.5% to 11% at screening (Visit 1) measured by the central laboratory at Visit 1 (screening)

5. Based on the Investigator's judgment patient with T1D 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 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
   - established "sick day" management regimen
6. Age ≥ 18 years at Visit 1
7. BMI of ≥ 18.5 kg/m^2
8. eGFR ≥ 60 ml/min/1.73m^2 as calculated by the CKD-EPI formula, based on creatinine measured by the central laboratory at Visit 1
9. Average BP > 90/60 mmHg and ≤ 140/90 mmHg 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 informed consent form

    *Women of child-bearing potential are defined as 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)

3.3.3 Exclusion criteria

1. For patients with T1D, treatment with an antihyperglycaemic agent (e.g. metformin, alpha-glucosidase inhibitors, pramlintide, glucagon-like peptide receptor agonist, etc.) within 3 months prior to Visit 1 or any history of clinically relevant hypersensitivity according to Investigator's judgment
2. Treatment with an SGLT-2i within 30 days of Visit 1
3. 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
4. Hypoglycaemia unawareness based on Investigator judgement or frequent episodes of unexplained hypoglycaemia (2 or more unexplained episodes within 3 months prior to Visit 1)

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

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

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

8. Diagnosis of brittle diabetes based on Investigator judgement

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

10. Requires the ongoing use of any concomitant medication known to interfere with the RAAS activity and/or renal function based on investigator judgement. Examples of restricted drug classes include ACEi, ARBs, aldosterone antagonists or renin inhibitors

11. Any contraindication to Altace® (ramipril) per local product monograph including the following:
    - History of angioedema
    - History of haemodynamically relevant bilateral renal artery stenosis or unilateral renal artery stenosis in a single kidney
    - History of hypotension or haemodynamically unstable states
    - History of hypersensitivity reaction to ramipril or to any other ACEi, or to any ingredient in the ramipril formulation

12. History of organ transplant, including pancreas, pancreatic islet cells or renal transplant

13. Surgical treatment for weight-loss or aggressive diet regimen leading to unstable body weight (based on Investigator's judgement) 3 months prior to Visit 1. For patients with T1D, use of anti-obesity drugs within 3 months prior to visit 1

14. 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

15. Change in dose of thyroid hormones within 6 weeks prior to Visit 1 or planned change or initiation of such therapy at Visit 1

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. Medical history of cancer or treatment for cancer five years prior to screening (Visit 1) with the exception of fully treated basal cell carcinoma

21. Patient not able to understand and comply with study requirements, based on Investigator's judgment

22. 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, patients who might be at higher risk of developing urinary, 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

Patients who discontinue treatment after randomisation will be considered as "early discontinuations" and the reason for premature discontinuation must be recorded in the Electronic Case Report Form (eCRFs). The data will be included in the trial database and will be reported.

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

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision
- The patient needs to take a forbidden concomitant therapy (as listed in Section 3.3.3 and Section 4.2)
- 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

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

For all patients the reason for withdrawal (e.g. AEs) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

If a patient becomes pregnant during the trial the investigational drug(s) 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.

Patients who drop out prior to randomisation (Visit 8) will be considered a screening failure. They have to be recorded as screening failure in eCRFs.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. 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 Boehringer Ingelheim. Insulin therapy is not considered to be part of the clinical trial supplies and therefore will not be provided by sponsor.

4.1.1 Identity of BI investigational product(s) and comparator product(s)

The characteristics of the test products are as shown below.

Substance	Empagliflozin (Jardiance®)
Pharmaceutical Form	Tablet
Source	Boehringer Ingelheim
Unit Strength	25 mg
Route of administration	Oral, once daily

Substance	Placebo matching empagliflozin 25 mg
Pharmaceutical Form	Tablet
Source	Boehringer Ingelheim
Unit Strength	-
Route of administration	Oral, once daily

Substance	ramipril (Altace®)
Pharmaceutical Form	Capsule
Source	or (commercial supply)
Unit Strength	5 mg
Route of administration	Oral, once daily during run-in. May be dosed twice daily during randomised treatment as prescribed by the Investigator

Substance	ramipril (Altace®)
Pharmaceutical Form	Capsule
Source	or (commercial supply)
Unit Strength	10 mg
Route of administration	Oral, once daily

Substance	ramipril (Altace®)
Pharmaceutical Form	Capsule
Source	or (commercial supply)
Unit Strength	1.25 mg
Route of administration	Oral, once or twice daily, as prescribed by the Investigator

4.1.2 Method of assigning patients to treatment groups

During Visit 8 and after the patient's eligibility has been confirmed based on the inclusion and exclusion criteria outline in Section 3.3.2 and Section 3.3.3, the treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

Patients will be randomly assigned to either Sequence A (25 mg empagliflozin followed by a 4 week wash-out period followed by matching placebo during period 2 dosing) or Sequence B (matching placebo followed by a 4 week wash-out period followed by 25 mg empagliflozin during period 2 dosing) in a 1:1 balanced ratio. Randomisation will not be stratified according to GFR. For further details please refer to Section 7.5.

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

4.1.3 Selection of doses in the trial

Ramipril treatment should be initiated at 5 mg q.d. and then titrated to 10 mg q.d. after one week. The 10 mg q.d. dose is the targeted dose. A lower dose ramipril (1.25 mg) will also be available if patients are not able to tolerate either the 10 mg or 5 mg ramipril dose. At the discretion of the Investigator, the patient may be prescribed a lower dose of ramipril if it is determined that the patient is unable to tolerate their current dose. Patients may take a lower dose including:

7.5 mg q.d.	5 mg q.d.
2.5 mg b.i.d.	2.5 mg q.d.
1.25 mg b.i.d.	1.25 mg q.d.

It is preferred that the dose of ramipril prescribed at the start of period 2 dosing is either the same dose used at the start of period 1 dosing or the maximum tolerated dose for ramipril. For example, if a patient starts period 1 dosing at 10 mg ramipril but is dose reduced to 5 mg q.d., 1 week into period 1 dosing, the patient should start period 2 dosing on the 10 mg ramipril dose or on their maximum tolerated dose of ramipril during wash-out. In this case, the up-titration of the ramipril dose should be done during the wash-out period. Lower doses of ramipril may be ordered through the IRT system.

Empagliflozin (25 mg) or matching placebo will be administered after randomisation during period 1 and period 2 dosing only. This dose was selected based on results from the previous trial that was conducted in patients with renal hyperfiltration [P13-16965].

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. All medication kits are to be ordered through the IRT. The open-label run-in period includes a dose titration from 5 mg ramipril to 10 mg ramipril after one week of treatment. After dose titration, all patients should remain on 10 mg ramipril for the duration of the study unless it is determined that the

patient is unable to tolerate the 10 mg dose. Patients who qualify to be randomised will be assigned to one of two treatment sequences through IRT:

- Sequence A: 25 mg empagliflozin in period 1 dosing followed a 4 week wash-out period followed by matching placebo in period 2 dosing
- Sequence B: matching placebo in period 1 dosing followed by a 4 week wash-out period followed 25 mg empagliflozin in period 2 dosing

Empagliflozin will be dispensed in a double-blind manner. During period 1 and 2 dosing and in the wash-out phase between each doing period, the patients will continue to take ramipril in an open label fashion.

Table 4.1.4:1 Oral administration of study medications per dose group

	Study Period	Ramipril 5 mg	Ramipril 10 mg	Empagliflozin 25 mg	Matching placebo to empagliflozin
Sequence A	Run-in	X			
	Run-in		X*		
	Period 1		X*	X	
	Wash-out		X*		
	Period 2		X*		X
Sequence B	Run-in	X			
	Run-in		X*		
	Period 1		X*		X
	Wash-out		X*		
	Period 2		X*	X	

*patients may take a lower dose of ramipril at Investigator's discretion (c.f. Section 4.1.3)

The 5 mg ramipril run-in medication will be dispensed by the Investigator or designee at visit 4a. The first administration of the ramipril medication should occur in the clinic under the supervision of the investigator or delegated site staff. The date and time of medication intake will be recorded in the patient diary.

The ramipril and empagliflozin / placebo medication to be taking during Period 1 dosing will be dispensed by the Investigator or designee at the end of visit 8 and the patient will be instructed to take their first dose of study medication in the morning of study day 1 (i.e. the following day). The date and time of medication intake will be recorded in the patient diary.

Patients should be instructed to take all study medication with water, with or without food. Ramipril (if dosed q.d.) and empagliflozin/ placebo should be taken once daily in the morning between 07:00 and 11:00, except when the patient has a clinic visit since the study medications will be administered in the clinic. To ensure a dose interval of approximately 24 hours, the medications should be taken at the same time every day. If a dose is missed by

more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled.

If a patient is prescribed a lower dose of ramipril that required twice daily dosing, then the ramipril medication should be taken in the morning (between 07:00 and 11:00) and in the evening (between 19:00 and 23:00). Patients should try to take their study medications at the same time each day except on days when the patient is scheduled to come into the clinic, as the study medications will be administered in the clinic. If a dose is missed by more than 6 hours, that dose should be skipped and the next dose should be taken as scheduled.

Patients are not permitted to take more than 10 mg of ramipril or take double doses or a lower dose of empagliflozin/placebo.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, the Investigator and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised empagliflozin or matching placebo treatment assignments until after database lock. The randomisation code will be kept secret by the Clinical Trial Support Group up to database lock.

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 drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

Due to the requirements to report 7 / 15 day reports, it may be necessary for a representative from BI's pharmacovigilance group to access the randomisation code for individual patients during study conduct. In such cases, access to the code will only be permitted by authorised pharmacovigilance representatives. Access to the code will be via an IRT system.

4.1.6 Packaging, labelling, and re-supply

Study medication (ramipril, empagliflozin, empagliflozin matching-placebo) will be provided by the . The study medication will be dispensed as indicated in the Flow Chart. The study medication will consist of containers labelled with the trial identification and medication kit number. Each container will contain an appropriate number of empagliflozin tablets (or placebo) or ramipril capsules with some reserve for dosing until the next scheduled visit.

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

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the CML (as provided in the list of contacts) must be contacted immediately.

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 trial protocol by the Institutional Review Board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the PI,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the PI

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, and the return to the Sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The 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, 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 return 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 formula:

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

Compliance during the open-label run-in period must be between 80% and 120 %. If complinace is outside of this range, the patient should be carefully interviewed and, if necessary, re-informed about the purpose and the conduct of the trial. Unreliable patients should not be randomised at the discretion of the Investigator.

Compliance during the randomised treatment 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 the 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 dicsussion should be documented.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Details of all concomitant therapy during the clinical trial will be recorded on the appropriate pages of the eCRF.

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

There are no rescue medications in this trial. Anti-hyperglycaemic therapy including insulin will not be provided as part of the clinical trial supplies.

Patients who are unable to tolerate (e.g. due to hypotensive side effect) the 10 mg dose of ramipril may be treated with lower doses of ramipril based on Investigator judgement (c.f. Section 4.1.3). Any patient who experiences a severe allergic reaction (e.g. angioedema) should immediately stop taking ramipril.

During periods of stability, in case of hypoglycaemia (e.g. with measured glucose concentrations ≤ 3.9 mmol/L), patients should preferably ingest additional carbohydrate according to standard practice in the management of diabetes. However a patient's existing diabetic 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 the previous trials in T1D (for further details see Section 1), at the start of Period 1 and Period 2 dosing, for T1D patients with an HbA_{1c} of < 8% at Visit 1, the Investigator is advised to reduce the patient's total insulin dose by 10% to avoid hypoglycaemia. For T1D patients with an HbA_{1c} of ≥ 8% at Visit 1, 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, further adjustments to insulin therapy may be implemented as necessary to avoid hypoglycaemia and 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 Period 1 and Period 2 dosing, and in the wash-out and follow-up periods, 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 the Investigator to follow 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, the Investigator must ensure that the patient with T1D 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. 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, insulin-dependent (T1D and T2D) patients treated with 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's 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, insulin-dependent patients with T1D or T2D 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 their glucose value in the event of DKA symptoms occurring. A meter will be provided to the patient for this purpose. Patients will be also 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. > 11.1 – 13.3 mmol/L) which cannot be explained. Regular (e.g., once daily) measurements before breakfast are recommended during period 1 and period 2 dosing and for 5 days after stopping the empagliflozin / placebo treatment. 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 the local treatment guidelines.

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

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Any treatment that is known to interfere with RAAS activity and/or renal function is strictly prohibited except for the ramipril study medication provided through the trial. Such medications include ACEi, ARBs, aldosterone antagonists and renin inhibitors or any other medication / drug class per Investigator judgement which may interfere with RAAS activity and/or renal function.

In patients with T1D, use of antihyperglycaemic drugs (e.g. metformin, other SGLT2i's, alpha-glucosidase inhibitors, pramlintide, etc.) other than insulin and the provided study medications should not be used during the trial including the follow-up period.

Use of other SGLT2i-s will be prohibited during the trial including the follow-up period.

Concomitant use of ramipril and extracorporeal treatments leading to contact of blood with negatively charged surfaces must be avoided as this may lead to anaphylactoid reactions. If such a treatment is required (e.g. dialysis or haemofiltration), the patient should be discontinued from the trial.

Treatment with anti-obesity drugs in patients with T1D or systemic steroids will be prohibited due to their influence on glucose metabolism. However, short-term use (i.e. ≤ 3 days duration) of systemic steroids, if deemed appropriate by the Investigator will be permitted as well as therapy with non-systemic steroids such as inhaled or local steroids. For patients taking thyroid hormones, any changes in the dose should be avoided. If a dose change does occur, then they should be recorded in the source documents and in the eCRF.

4.2.2.2 Restrictions on diet and life style

At the screening visit, patients will receive diet and exercise counselling by the Investigator or qualified site personnel. The counselling will be based on local diet recommendations for the patients with T1D in consideration with each patient's possible concomitant illnesses. Site specific tools may be used to help patients with diet and lifestyle / exercise counselling. The patients will be reminded to follow the recommended diet and exercise plan during the study. Patients are also requested to adhere to a specific sodium rich (preferably > 140 mmol/day) and moderate-protein (<1.5 g/kg/day) diet only during the 7 days preceding the start of the renal physiology laboratory assessments (7 days before study days -42, -1, 28 and 84). Details of this specific diet will be given to patients at Visit 1 and patients will be reminded to re-start this diet via a phone call approximately 7 days prior to study Days -42, -1, 28 and 84).

Patients should not participate in strenuous physical activity that requires significant changes to their diet and insulin during the run-in and treatment periods. Extreme diets (e.g. ketogenic diets) should be avoided.

Women of child-bearing potential must use a highly effective method of birth control (in accordance with the trial exclusion criteria cf. Section 3.3.3) throughout the duration of the study, including the follow-up period.

Patients must not take any other investigational drug within 30 days before Visit 1 until the last visit (Visit 16) of this trial.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

None of the endpoints are a known safety issue.

5.1.1 Primary Endpoint(s)

The primary endpoint is GFR under euglycaemic conditions after 4 weeks of treatment with either empagliflozin added to ramipril or placebo added to ramipril.

5.1.2 Secondary Endpoint(s)

Filtration status (GFR < 120 mL/min/1.73m^2; yes/no) after 4 weeks of treatment with either empagliflozin added to ramipril or placebo added to ramipril.

5.2 ASSESSMENT OF EFFICACY

5.2.1 Haemodynamic measurements

For all experimental phases, blood glucose will be monitored routinely in obese (non-diabetic) patients to ensure that plasma glucose is between 4 – 6 mmol/L. In all diabetic patients and those obese patients with elevated blood sugar (i.e. > 6 mmol/L), blood glucose is maintained by a modified glucose clamp technique, as previously described [R10-6374]. In summary, a 16-gauge peripheral venous cannula is inserted into the left antecubital vein for

infusion of glucose and insulin and more distally, a second cannula is inserted for blood sampling. Blood glucose is measured every 10–15 min, and the insulin infusion is adjusted to maintain the desired glycaemic index. Experiments are performed in the same temperature controlled room and in a dark, quiet environment after 10 min of rest in the supine position.

Renal and systemic vascular function assessments are performed at baseline (visit 4) and then repeated in an identical fashion at the end of each period dosing (visit 8, 11 and 15). Following arterial stiffness assessments (more details in Section 5.2.3), an intravenous line is inserted into the right arm and is connected to a syringe infusion pump. In the first 31 randomized patients in the trial, inulin and paraaminohippurate (PAH) was administeredafter collection of blood for inulin and PAH blank. A priming infusion containing 25% inulin (60 mg/kg) and 20% PAH (8 mg/kg) is administered. Thereafter, inulin and PAH are infused continuously at a rate calculated to maintain their respective plasma concentrations constant at 20 and 1.5 mg/dl. After a 90-min equilibration period, blood is collected for inulin, PAH, and haematocrit. Blood is also collected as applicable every 30 mins for inulin, PAH and haematocrit measurements. GFR and ERPF are respectively estimated by steady-state infusion of inulin and PAH [R10-6364].

In the remaining patients entered into the trial, a bolus infusion of iohexol is administered approximately 2 hours prior to the infusion of 20% PAH (8 mg/kg) [R18-1807, R18-1808]. PAH is infused continuously at a rate calculated to maintain a plasma concentration of 1.5 mg/dl. GFR and ERPF are estimated based on concentrations of iohexol and PAH based on blood sample collections at the following time points:

Time Point	Activity
0	Iohexol (pre-dose) plasma sample collection Iohexol infusion
+120 min	PAH (pre-dose) sample collection PAH infusion Iohexol plasma sample collection Haematocrit sample collection
+150 min	Iohexol plasma sample collection Haematocrit sample collection
+180 min	Iohexol plasma sample collection Haematocrit sample collection
+ 210 min	Iohexol plasma sample collection PAH sample collection Haematocrit sample collection
+240 min	Iohexol plasma sample collection

	PAH sample collection Haematocrit sample collection

5.2.2 Segmental tubular handling of sodium

Tubular sodium handling will be assessed using an established sodium and lithium clearance technique [R15-3481, R15-3480]. Approximately 12 hours prior to renal assessment visits (Visits 4, 8, 11 and 15); patients will be required to take 300 mg lithium orally. During renal assessment visit, after euglycaemia equilibrium has been achieved, blood and urine samples for sodium, lithium and creatinine will be collected at 3 time-points. The estimated proximal fractional fluid re-absorption rate and the estimated absolute distal sodium delivery can be calculated based on the urinary lithium, sodium clearances, GFR and the lithium and sodium fractional excretion rates.

5.2.3 Arterial stiffness and sympathetic nervous system (SNS) measurements

Augmentation index (AIx) for the radial and carotid arteries as well as a derived aortic AIx and carotid, radial and femoral pulse wave velocities will be measured for assessment of arterial stiffness when feasible using a SphygmoCor® System, and necessary software or a similar instrument based on previously published methodologies [R11-0072]. Such an instrument allows a non-invasive means of quantifying cardiac autonomic activity allowing assessment of sympathetic and parasympathetic autonomic function including variable heart rate which will be measured as part of the SNS assessments. The SphygmoCor® System provides a comprehensive assessment of the key cardiac parameters including central BP, arterial stiffness and autonomic function and calculates both time and frequency domain heart rate variability parameters, including the vagal index. The use of the SphygmoCor® System for assessment of arterial stiffness and endothelial function has been previously validated [R10-6380].

5.2.4 Blood pressure (BP) and pulse rate

5.2.4.1 Routine clinic visits

The initial reading of BP at screening (Visit 1) should be done in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), the arm with the higher pressure (systolic or if needed to decide, diastolic) should be used for subsequent measurements.

BP measurements should be performed on the same arm after the initial assessment and, if possible, by the same person. The same method and device must be used throughout the trial for a patient.

For routine vital sign assessments (not at visits 4, 8, 11 and 15), systolic and diastolic BP as well as pulse rate will be measured after 5 minutes of rest in the supine position. The BP measurement should be performed three times and all three measurements will be entered in the eCRF. The second and third BP measurements will be done respectively 2 minutes and 4

minutes after the initial measurement. The pulse rate measurement will be done during the 2nd and 3rd BP measurement after a full minute count.

5.2.4.2 Renal study visits

BP and pulse rate measurements will be made using an automated Dinamap sphygmomanometer. Measurements will be taken in the supine position during the renal study days (visit 4, 8, 11 and 15). An average of three measurements will be recorded and used to calculate renal haemodynamic parameters following the procedure outlined in section 5.2.4.1. BP measurements should be recorded to the nearest 2 mmHg only when measured with a manual sphygmomanometer; when digital devices are used, the value from the device should be rounded to the nearest 1 mmHg.

5.2.5 Weight and waist circumference

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

- After the urine sampling (weigh after bladder voiding)
- Shoes and coats/jacket should be removed
- Pockets should be emptied of heavy objects (e.g. keys, coins, etc.)

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

Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest.

5.2.6 Ambulatory blood pressure monitoring

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

At each ABPM visit (Visits 3, 7, 10 and 14), patients are to come to the clinic and the following procedure will be performed.

- The ABPM monitor will be attached to the patient and checked to see if it is working properly prior to medication intake (except visit 3).
- Once it has been confirmed that the monitor is properly functioning, study medication will be administered followed by prompting of the monitor to take the Beginning of Test reading.
- Record the time the medication was administered and the time the monitor was prompted to take the Beginning of Test reading.

- The next day when the patient returns to the clinic, the monitor will be prompted to take a Conclusion of Test reading. The device will then be removed and the time of the Conclusion of Test will be recorded. This should be done preferably within 22-24 hours of starting monitor.

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

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

5.2.7 Non-invasive cardiac output monitoring

Cardiac output, stroke volume and total peripheral resistance will be derived from stroke volume and heart rate that is measured using the Non-Invasive Cardiac Output Monitoring (NICOM®) system (Cheetah Medical Inc.) under conditions of euglycaemia at visits 4, 8, 11 and 15. The NICOM® monitoring system is based on Bioreactance® technology [R15-3482]. Four sensor pads will be applied above and below heart on the chest. Each sensor pad contains an outer transmitting sensor and an inner receiving sensor. The NICOM® monitor induces a 75KHz AC current to the thorax via the outer sensors and receives the voltage via the inner sensors. The sensors can detect a time delay or phase shift between the induced current and the received voltage. Stroke volume is derived based on consecutive measurements of the phase shift.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A complete physical examination will be performed by the Investigator or designated site personnel at the time-points 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 (SBGM)

From the beginning of the trial (Visit 1) until the end of the follow-up period (Visit 16), all patients with diabetes (T1D or T2D) will be provided with SBGM equipment (i.e., a glucose monitoring device / meter) and supplies for use at home and at the site during the study for SBGM. Instructions on the proper use of the SBGM equipment will be provided by the site staff. The patient will be asked to record the results of the SBGM test on a log that will be included in the patient's source document file. Only in the case of linked AEs or of hypoglycaemia, will glucose levels from the SBGM be documented in the eCRF. Obese patients who do not have diabetes are not required to monitor blood glucose unless deemed necessary by the investigator.

Patients with T2D, SBGM testing should be performed at least once per day as a minimum or more frequently as recommended by the Investigator or at any time when the patient is experiencing symptoms of hypo- or hyperglycaemia.

For patients with T1D, SBGM testing should be performed 4 times a day as a minimum (i.e. at least before breakfast, lunch, dinner and at bedtime); furthermore, for 5 days after randomisation to empagliflozin / placebo, SBGM testing frequency should be increased to 8-10 times a day and include at least one overnight measurement. Additional tests should be done as recommended by the Investigator 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. > 6.1 – 7.2 mmol/L (>110 – 130 mg/dL) should be targeted at bedtime to avoid nocturnal hypoglycaemia. The sponsor will also provide guidance on this topic via documentation in the ISF.

For patients with diabetes, if, after an overnight fast, a SBGM test result reveals blood glucose of > 11.1 - 13.3 mmol/L (200 – 240 mg/dL) or < 3.9 mmol/L (70 mg/dL), 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).

The same SBGM system will be supplied to all patients with diabetes and must be used by the patient throughout the study. In accordance with Section 3.3.2, the Investigator 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 re-trained at the earliest possible opportunity.

5.3.2.2 Ketone monitoring

Patients with T1D or patients who are only using insulin for management of diabetes will be provided 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 with T2D, who are managed with oral anti-hyperglycaemic agents only, or obese patients, are not required to monitor their ketones unless requested to do so by the investigator.

Patients should measure their ketones at least one daily, ideally after fasting for at least 6 hours, throughout the Period 1 and Period 2 dosing, including for 5 days after empagliflozin / placebo treatment has been stopped. Patients should be reminded to test their ketones in case of any symptoms of DKA, e.g. nausea, vomiting, and abdominal pain. 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. >11.1 mmol/L (> 200 mg/dL)) which cannot be explained.

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 or temporarily discontinue study drug) or contact their trial site. Blood glucose and ketone levels should be checked every 1-2

hours until they are back in a range considered to be normal. 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 a blood gas test (pH, bicarbonate) should be performed locally at the earliest opportunity. The results will be collected on the relevant page of the eCRF.

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.

5.3.2.3 Blood Pressure

Patients will be provided with a personal BP monitor at visit 4a for use at home. Instructions on the proper use of the equipment will be provided by the site staff. Only in the case of linked AEs, will the BP readings be documented in the eCRF.

Routinely, BP monitoring should be performed twice a day (i.e. morning and at bedtime). Additional tests should be done as recommended by the Investigator or at any time the patient is symptomatic, i.e. feels light-headed or experiences postural hypotension.

If BP values repeatedly fall below 90/60 mmHg, the patient should contact the site immediately.

5.3.3 Safety laboratory parameters

All safety and efficacy laboratory samples will be collected according to the summary of assessments in Table 5.3.3:1 and Table 5.3.3:2 below. The Flow chart specifies which visits should be conducted when the patient is fasting. Laboratory samples should be collected before the administration of study medication as described in the Flow Chart. Patients should continue to take their prescribed medications as instructed by the prescribing physician.

The analysis of the safety laboratory parameters 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.

Table 5.3.3: 1 Safety laboratory parameters

Haematology:

- Haematocrit
- Haemoglobin
  - Reticulocyte Count (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

Table 5.3.3:1 Safety laboratory parameters, continued

Clinical chemistry:

- Albumin
- Alkaline phosphatase
  - Gamma-glutamyl transferase (γ-GT, reflex test triggered by elevated AP on two sequential measures)
- ALT (alanine aminotransaminase, SGPT)
- AST (aspartate aminotransaminase, SGOT)
- Beta-hydroxybutyrate (BHB)[1]
- Bicarbonate
- Bilirubin total (fractionated if elevated)
- Calcium
- Chloride
- Creatinine
- Creatine kinase (CK)
  - hs troponin T (reflex tests if CK is elevated)
- C-peptide[2] (performed at screening only in T1D patients only)
- Lactate dehydrogenase
- Lipase
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- Blood urea nitrogen
- Uric acid

Lipids:

- Cholesterol (total)
- HDL cholesterol
- LDL cholesterol
- Triglycerides

Other assessments at selected visits:

- Thyroid stimulating hormone[2] (TSH) (screening only)
- Glycated haemoglobin (HbA_{1c})
- Fasting plasma glucose (FPG)
- Human Chorionic Gonadotropin (hCG)[3]

Table 5.3.3:1 Safety laboratory parameters, continued

Urinalysis:

Dipstick (A):
Immediate site assessment for leukocyte and/or nitrite[4]
Routine urinalysis (B):

- Glucose
- Ketone
- Specific Gravity
- Blood
- Urine pH
- Protein
- Nitrite
- Leukocyte/Leukocyte esterase

Quantitative (C):

- Albumin[2]
- Creatinine[2]
- Alpha-1 microglobulin
- BHB[1]

24 hour urine collection:

- Sodium, glucose, BHB[1], urea and creatinine

1. BHB to be tested at visits 1, 4, 8, 11, 12 and 15. At visits 4, 8, 11, and 15 blood and urine samples are to be collected within 30 minutes of starting the inulin or iohexol and PAH infusion and also between 1.5 and 2 hours after the study medication has been administered.
2. Visit 1 safety lab tests will include haematology, chemistry, C-peptide (only in T1D patients) TSH (only measured at visit 1) and routine urinalysis B. Urine albumin and creatinine to be measured at visit 1 including calculation of the albumin/creatinine ratio.
3. Pregnancy testing (serum) will be performed in female patients of child bearing potential at specified visits in the flow chart. Additional tests may be done if locally required and per Investigator judgement.
4. A mid-stream urine sample must be sent for culture upon a positive leukocyte and/or nitrite assessment based on dipstick at the site or upon Investigator suspicion of a UTI.

An eGFR will be derived from serum creatinine values at visit 1 and visit 8 based on the CKD-EPI formula which is considered to be more accurate in the normal range than the Modification of Diet in Renal disease formula. The CKD-EPI formula will be defined in the central laboratory documentation due to the regional / racial variations in the formula that is applied.

The following renal analysis will be completed at visit 4, 8, 11 and 15 (under euglycemic conditions). Inulin and PAH analysis will be performed by the local laboratory.

Table 5.3.3: 2 Renal analysis

Renal panel (plasma samples):

- cGMP
- Nitric oxide
- Angiotensin II (RAAS mediator)
- Angiotensinogen (RAAS mediator)
- Aldosterone (RAAS mediator)
- Plasma renin activity (RAAS mediator)
- Plasma renin concentration (RAAS mediator)
- Inulin or Iohexol
- Lithium
- Paraaminohippurate (PAH)
- 8-hydroxydeoxyguanosine
- 8-isoprostane

Quantitative urinalysis (C):

- cGMP
- Nitric oxide
- cAMP
- Lithium
- 8-hydroxydeoxyguanosine
- 8-isoprostane

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 tract infection at screening will be identified and this condition must be documented as a 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 antibiotics should be provided as appropriate.

For documentation of acute UTI during the 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 time-points indicated in the Flow Chart. In case of a positive result at the site, a urine culture 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 baseline and at the end of the trial for all patients. In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischemia), an additional ECG will be recorded. All ECGs will be evaluated, (signed, dated and commented upon) by the 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 the central laboratory measurements. Glucose values originating from the SBGM device will subsequently be entered into the patient diary.

5.3.5.2 Criteria for hypoglycaemic events

Every episode of plasma glucose below or equal to 3.9 mmol/l (70 mg/dl) should be documented with the respective time and date of occurrence. This includes any hypoglycaemia with glucose values <3.0 mmol/l (<54 mg/dl) and all symptomatic and severe hypoglycaemias.

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 plasma glucose concentration ≤3.9 mmol/l (≤70 mg/dl)
- Documented symptomatic hypoglycaemia with glucose concentration ≥3.0 mmol/l and ≤3.9 mmol/l (≥54 mg/dl and ≤70 mg/dl): Event accompanied by typical symptoms of hypoglycaemia
- Documented symptomatic hypoglycaemia with glucose concentration <3.0 mmol/l (<54 mg/dl): Event accompanied by typical symptoms of hypoglycaemia but no need for external assistance

- Severe hypoglycaemic episode: Event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. 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 T1D care, it is advisable for the patient to carry this throughout the trial.

5.3.5.3 Criteria for diabetic ketoacidosis

Refer to Section 5.3.6.1.

5.3.6 Assessment of Adverse Events

5.3.6.1 Definitions of AEs

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

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

Adverse reaction

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

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

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  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 jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

AEs considered "Always Serious"

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

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

The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above and in Section 5.3.7.

Adverse events of special interest (AESIs)

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

Patients with AESIs need to be followed up appropriately, regardless of the origin of the laboratory data (e.g., central or local lab, 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 run-in (Visit 4):

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

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

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

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 is defined by the diagnostic criteria in Table 5.3.6.1:1 below, and as defined by the ADA [R14-5435].

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

Table 5.3.6.1: 1 Diagnostic Criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma glucose (mg/dL / mmol/L)	>250 / 13.9	>250 / 13.9	>250 / 13.9
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
Mental status	Alert	Alert / drowsy	Stupor / coma

*Nitroprusside reaction method
**calculation: 2[measured NA (mEq/L)] + glucose (mmol/L)
***calculation: $(Na^+) – [Cl^- + HCO_3^-$ (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.

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

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

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.

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative etiologies that could explain the event (e.g. preexisting or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.3.7 Adverse event collection and reporting

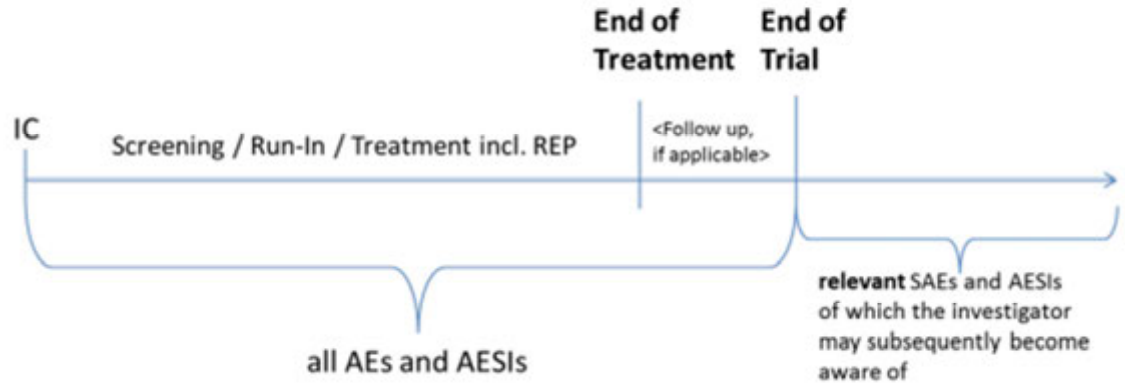
AE Collection
The Investigator shall maintain and keep detailed records of all AEs in their patient files.

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

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

- all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of trial:
  the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.



The REP is defined as 7 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

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

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

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s).

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

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

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

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

Pregnancy
In rare cases, pregnancy may occur in a clinical trial. Once a subject has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately within 24 hours) a potential 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).

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

Additional, optional, blood and urine samples will be collected at visits 4, 8, 11 and 15 for the analysis of exploratory biomarkers. These samples will be stored for up to 15 years after the

end of the clinical trial and may be used for future exploratory analyses. Samples will be shipped from the site to the central laboratory for short term storage. These samples will be shipped in batches to BI or to a location where the analysis of biomarkers will be conducted or the samples will be stored.

5.5.1 Endpoints based on biomarkers

Not applicable.

5.5.2 Methods of sample collection

Blood and urine samples will be collected from patients who provide consent to the optional biomarker sample collection. A detailed description of sample collection, handling and shipment will be provided in the ISF / lab manual.

5.5.3 Analytical determinations

After completion of the study, banked blood and urine samples may be used for further investigations, e.g., identification of novel biomarkers associated with cardio-metabolic or renal disease. The different exploratory biomarkers will be analysed using fit-for-purpose validated assays at Boehringer Ingelheim or contracted laboratory vendor.

5.5.4 Biobanking

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

Measurements performed during this trial are standard or previously validated measurements and will be performed in order to monitor safety aspects and to determine PDs in an appropriate way.

The scheduled measurements are appropriate to see drug-induced changes in vital signs, standard laboratory values, ECG, biomarkers specific to efficacy of treatment of T1D and renal endpoints. The primary and other endpoints are acceptable evaluations of safety and tolerability of an oral anti-diabetic drug.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits should take place preferably between 7:00 AM and 11:00 AM (except Visits 4, 8, 11 and 15). If a patient mistakenly takes the trial medication on the morning of a schedule visit before attending the clinic or comes in non-fasted where a fasting condition is required, the visit should be rescheduled for another day if possible and the patient should be reminded about the expected conditions when presenting at the clinic. The rescheduled visit must take place in a short enough time-frame so that the patient has sufficient trial medication available.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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 and run-in period(s)

Screening Period

- No trial procedures should be done unless the patient has consented to taking part in the trial. Once consent has been obtained, 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
- Screening procedures may be conducted over several days within the screening window.
- If a patient is taking a RAAS inhibitor and may safely discontinue, in the opinion of the investigator, patients may commence a wash-out of their prescribed RAAS inhibitor after signing the informed consent form for study participation. Screening lab results may also be reviewed prior to commencing RAAS wash-out, at the discretion of the investigator. Patients must not take the prescribed RAAS inhibitor for a minimum of 2 weeks prior to commencing with visit 2 activities. During the wash-out period, if the patient need to re-start their prescribed RAAS inhibitor therapy, the patient must be screen failed.
- A lab test may be repeated during the screening period if the lab results were not provided by the central lab (e.g. the lab test was deleted) or if the lab results are inconsistent with the patient's medical history.
- BP should always be taken before any blood samples are taken. Refer to Section 5.2.4.
- A glucose / ketone meter with all the necessary supplies for home monitoring of glucose and ketones will be given to patients with T1D or patients who use insulin to manage their diabetes. T2D patients who manage their diabetes with anti-hyperglycaemic agents, other than insulin, will be provided with a glucometer and required supplies. Ketone strips may be provided if ketone monitoring is deemed necessary by the investigator. Site staff must provide instruction on how to use the meter. Patients will be provided with a diary to record values (to be completed daily).

- Dietary requirements for the trial should be discussed at Visit 1. Patients will be instructed to follow a healthy diet and exercise program during the course of the study except from the 7 days prior to renal assessments. Patients should understand that they will need to follow the modified (sodium rich, moderate protein) diet for 1 week preceding the renal assessments.
- Visit 2 can be conducted as a phone visit. Site staff should remind the patient to start the modified diet.
- 24 hour urine collection and ABPM must be performed after the patient has been following the modified diet but prior to the renal assessments. It is recommended that the patient return to the clinic on the following day to return the urine collection container and to remove the ABPM device. If the patient is not able to return to the clinic, the site staff must instruct the patient on how to remove the ABPM device and how to properly store the urine collection container.
- One day prior to the renal assessments, the patient must take a 300 mg lithium tablet with a small amount of water. Site staff should provide the lithium tablet to the patient when the patient is in the clinic to have the ABPM device attached.
- Renal assessments will be performed one day prior to start of open label ramipril treatment. Patients should report to the renal physiology lab by 7:30 am.
- After all renal assessments have been completed at visit 4, run-in medication must not be dispensed until after the GFR results are available (i.e. at visit 4a). The patient may be included in the run-in if the patient's GFR from visit 4 is ≥135 ml/min/1.73m^2 or if enrolment of normofilterer patients is still permitted (refer to section 3.3).

Run-in Period

- At visit 4a, the site staff should contact the IRT to obtain a ramipril kit number. Ramipril administration should occur while the patient is in the clinic by the investigator or delegated site staff.
- Patients will receive a home BP monitor so that they may monitor their BP while taking the study medications. Site staff must provide instruction on how to use the device. BP readings may be recorded in the patient diary.
- After the start of ramipril treatment and following dose titration to 10 mg ramipril, site staff should contact the patient daily for approximately 5 days to ensure that the patient is tolerating the dose adjustment.
- An unscheduled visit may be performed if the patient is experiencing side effects to the ramipril treatment. At the discretion of the Investigator, a lower dose of ramipril may be ordered through the IRT.
- One day prior to the renal assessments, the patient must take a 300 mg lithium tablet with a small amount of water. Site staff should provide the lithium tablet to the patient when the patient is in the clinic to have the ABPM device attached.
- At visit 8 after all renal assessments have been completed, the patient's eligibility should be confirmed and eligible patients should be randomised to treatment through the IRT. The site staff should dispense the study medication and instruct the patient not to take the study medication (ramipril and empagliflozin /placebo) until the following morning (i.e. Day 1). The patient should be instructed to record the actual date and time of medication in-take in their patient diary.

- During the recruitment phase of the study, close monitoring of baseline GFR (at visit 8) will be done to ensure that clinically, a sufficient number of patients with renal hyperfiltration are included in the study.

6.2.2 Treatment period(s)

6.2.2.1 Period 1 dosing

- It is recommended that the patient should not initiate double-blind treatment with empagliflozin/placebo if the patient is unwell (i.e., experiencing an acute illness like a flu or cold). Treatment should be delayed until the patient has recovered from the acute illness.
- If the patient was unable to tolerate the 10 mg ramipril dose during run-in, the patient may continue on the lower dose throughout the treatment period including the wash-out period.
- Starting Day 1 and for approximately the next 5 days, patients must be followed up daily (phone calls) to ensure that all study safety and efficacy procedures are adequately followed.
- Visit 9 may be completed as a phone visit. Patients should be instructed to start their modified diet one week prior to the renal assessments.
- The 24 hour urine collection and ABPM should be performed once the patient is on the modified diet and at least 24 hours prior to the start of the renal assessments.
- One day prior to the renal assessments, the patient must take a 300 mg lithium tablet with a small amount of water. Site staff should provide the lithium tablet to the patient when the patient is in the clinic to have the ABPM device attached.
- At visit 11, all study medications should be returned to the clinic. The IRT system will assign a new ramipril kit to be taken during the wash-out period.

6.2.2.2 Wash-out

- Starting Day 29 and for approximately the next 5 days, patients must be followed up daily (phone calls) to ensure that all study safety and efficacy procedures are adequately followed.
- If the patient's ramipril dose was down titrated during Period 1 dosing, the patient's ramipril dose should be up-titrated during the wash-out period to their maximum tolerated dose which ideally is the same dose of ramipril that they started Period 1 dosing with.
- Visit 12 will be at the end of the wash-out period. At this visit, ramipril from the ramipril kit dispensed at the previous visit should be administered to the patient prior to collecting the kit.
- A new ramipril kit and empagliflozin/placebo kit will be assigned via IRT. The site staff should dispense the study medication and instruct the patient not to take the study medication (ramipril and empagliflozin /placebo) until the following morning (i.e. Day 57). The patient should be instructed to record the actual date and time of medication in-take in their patient diary.

6.2.2.3 Period 2 dosing

- It is recommended that the patient should not initiate double-blind treatment with empagliflozin/placebo if the patient is unwell (i.e., experiencing an acute illness like a flu or cold). Treatment should be delayed until the patient has recovered from the acute illness.
- The patient should start Period 2 with the same ramipril dose that they were on at the start of Period 1 dosing or their maximum tolerated dose during wash-out (refer to Section 4.1.3).
- Starting on Day 57 and for approximately 5 days, patients must be followed up daily (phone calls) to ensure that all study safety and efficacy procedures are adequately followed.
- Visit 13 may be completed as a phone visit. Patients should be instructed to start their modified diet one week prior to the renal assessments.
- The 24 hour urine collection and ABPM should be performed once the patient is on the modified diet and at least 24 hours prior to the start of the renal assessments.
- One day prior to the renal assessments, the patient must take a 300 mg lithium tablet with a small amount of water. Site staff should provide the lithium tablet to the patient when the patient is in the clinic to have the ABPM device attached.

6.2.2.4 Unscheduled visits during the treatment period

- At any point in time during the study, an unscheduled visit may occur to ensure patient safety.
- If the patient is experiencing hypotension or other side effects known to occur with ramipril treatment, the patient may come for an unscheduled visit and have a dose adjustment. 7.5 mg or 5 mg b.i.d. should be tried initially so that the total daily dose remains unchanged. If side effects persist with a 10 mg total daily dose, the patient may be further down titrated. All medication kits should be ordered through the IRT.
- Select study procedures may be performed at these visits per Investigator judgement. These procedures may include, but are not limited to, additional safety laboratory tests, vital signs, physical examination, diabetes diet and exercise counselling or insulin dose adjustment.

6.2.3 Follow Up Period and Trial Completion

- The final treatment visit is visit 15. All study medications must be returned at visit 15. All patients should return to the clinic for their final follow-up visit (visit 16).
- Although patients have stopped taking the study medications, the patients should be contacted by phone for approximately 5 days, to ensure that all study safety procedures are adequately followed.

6.2.3.1 Early end of treatment visit (eEOT)

- The eEOT visit is only required for those patients who discontinue from the trial early.
- If a patient discontinues from the trial early (after the start of ramipril study medication), an eEOT visit should be done as soon as feasible.

- These patients should return to the clinic for an additional follow up visit (Visit 16). If feasible, early discontinued patients should continue with SBGM until Visit 16.
- All AEs should be collected until the end of the REP (i.e., 7 days after the last medication intake) for patient who discontinue from treatment early. Refer to Section 5.3.7.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This is a randomised, double-blinded, placebo-controlled 2x2x2 (2-treatment, 2-sequence, 2-period) crossover, single-centre trial.

The primary objective is to assess the effect of the addition of empagliflozin to ramipril on reducing GFR in patients with T1D, T2D or obesity who have GFR ≥ 135 mL/min/1.73 m^2 (under euglycaemic conditions) after ramipril monotherapy.

Patients who successfully complete the open-label ramipril run-in period and meet the inclusion/exclusion criteria will be randomised into the trial, with no stratification, to one of two sequences; empagliflozin-placebo (A) or placebo-empagliflozin (B).

Efficacy analysis of this trial will be based around four subgroups of patients defined by baseline GFR measurements under euglycaemic conditions:

- Hyperfilterers: Patients before ramipril monotherapy with GFR ≥ 135 mL/min/1.73 m^2, as measured at screening (visit 4)
- Non-responders: Patients after ramipril monotherapy with GFR ≥ 135 mL/min/1.73 m^2, as measured at randomisation (visit 8)
- Responders: Patients after ramipril monotherapy with GFR < 135 mL/min/1.73 m^2, as measured at randomisation (visit 8)
- Normofilterers: Patients before ramipril monotherapy with GFR < 135 mL/min/1.73 m^2, as measured at screening (visit 4)

Note Non-responders and Responders are a subset of the Hyperfilterers.

These subgroup definitions will be used throughout. The primary efficacy analysis of this trial will be based around the hyperfilterers subgroup. Secondary and further efficacy analysis will focus on the other subgroups and overall. Safety analysis will primarily focus upon all treated patients, but secondary analysis by GFR subgroup will also be performed.

Restricted Maximum Likelihood Estimation (REML) based Mixed-effects Model for Repeated Measures (MMRM) analysis will be used to obtain adjusted means for the treatment effects. This model will include treatment and period as fixed effects, patient as a random effect and randomisation baseline (visit 8) as a covariate. Compound symmetry will be used as a covariance structure for within-patient variation.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Let μ_{HA} be the mean GFR under euglycaemic conditions after 4 weeks of treatment with ramipril and empagliflozin combination therapy in hyperfilterers.

Let μ_{HB} be the mean GFR under euglycaemic conditions after 4 weeks of treatment with ramipril and placebo combination therapy in hyperfilterers.

Primary Objective Hypothesis:

The primary objective of the trial will be addressed by a two-sided test at level $\alpha = 0.05$. The following null and alternative hypotheses will be tested:

H_0: $\mu_{HA} - \mu_{HB} = 0$

H_1: $\mu_{HA} - \mu_{HB} \neq 0$

The test of the null hypothesis will be supported by the 95 % confidence interval (CI) for $\mu_{HA} - \mu_{HB}$ and the null hypothesis will be rejected if the CI excludes 0 mL/min/1.73 m^2.

7.3 PLANNED ANALYSES

Patients have been shown previously to respond differently to ramipril or empagliflozin depending upon their baseline GFR measurement [R10-6368], ATIRMA, [c01802271-02]. In particular, differential changes from baseline have been demonstrated above and below 135 mL/min/1.73m^2. The variance in the response without baseline adjustment has also been previously shown to vary with baseline GFR [c01802271-02].

Therefore, patients will be principally analysed by GFR subgroups, defined using GFR measurements at screening (visit 4) and randomisation (visit 8). Responder/non-responder subgroups will be defined using the randomisation measurement, which is on ramipril treatment. Normofilterer/hyperfilterer subgroups will be defined using the screening measurement, which is pre-ramipril treatment. The subgroup definitions are provided in Section 7.1. In general, efficacy analysis of this trial will be conducted by subgroup, although analysis will also be conducted across the full set. If patient numbers are too low to allow a meaningful analysis for a subgroup then only a descriptive summary will be presented.

It should be noted that despite analysis being conducted by GFR status, no GFR-based stratification is performed at randomisation due to the length of time required for GFR results to be obtained. This is viewed to not be problematic as the crossover design ensures that balance is maintained between treatments within each subgroup. Randomisation will ensure that approximate balance is likely between sequences within subgroups and complete balance is not viewed as necessary as no sequence-related effects are foreseen.

The statistical analysis will be based on the following populations:

Run-In Set (RIS)

The run-in set (RIS) will consist of all patients who were treated with at least one dose of study drug (ramipril, empagliflozin and/or placebo).

Treated Set (TS)

The treated set (TS) will consist of all patients who were randomised and treated with at least one dose of empagliflozin/placebo.

Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all patients who were randomised, treated with at least one dose of empagliflozin/placebo and provided randomisation baseline (visit 8) and at least one post-randomisation GFR measurement.

Per Protocol Set (PPS)

There will be a per protocol set (PPS), the inclusion/exclusion criteria for which will be fully defined in the TSAP.

Where subgroups of these sets are analysed, the subgroup will be described within the analysis description.

Patients will be analysed for efficacy according to the randomised treatment rather than the treatment actually received.

7.3.1 Primary endpoint analyses

7.3.1.1 Primary Analysis

The primary analysis of the primary endpoint will be performed upon the hyperfilterer subgroup of the FAS. Therefore, all randomised hyperfilterer patients (visit 4, GFR ≥ 135 mL/min/1.73 m^2 under euglycaemic conditions) who were treated with at least one dose of empagliflozin/placebo, had a randomisation (visit 8) baseline and at least one on-treatment GFR measurement will be included.

Comparisons between treatment groups for the primary endpoint will be based on a mixed effect repeated measures model (MMRM). This model will include treatment and period as fixed effects, patient as a random effect and (randomisation) baseline as a covariate. Compound symmetry will be used as a covariance structure for within-patient variation. The SAS procedure MIXED will be used involving the REML estimation method and the Kenward-Roger approximation for denominator degrees of freedom and standard error adjustment. This approach is described in Kenward and Roger [R10-4391]. Adjusted mean values as well as treatment contrasts will be presented together with the 95% CIs and p-values.

The model is described by the following equation:

$Y_{ij} = \alpha_i + \pi_j + \tau_{ij} + \beta S_i + \varepsilon_{ij}$, where

Y_{ij} = GFR measured on patient i in period j,

α_i = the random effect associated with the i'th patient, i = 1, 2, ..., n,

π_j = the j'th period effect, j = 1, 2,

τ_{ij} = the effect of treatment applied to patient i in period j,

β = a fixed model coefficient,

S_i = baseline GFR for patient i,

ε_{ij} = the random error associated with the i'th patient in period j.

Baseline GFR will be defined as the GFR measurement obtained at randomisation (visit 8). The random errors ε_{ij} are assumed to be independent, normally distributed with mean 0 and unknown variance σ_ε^2. The random effects α_i are assumed to be independent, normally distributed with mean 0 and unknown variance σ_α^2. ε_{ij} are also assumed to be independent of α_i.

7.3.1.2 Secondary and sensitivity analyses

- The following patient populations will be analysed using the same statistical methods as described for the primary analysis in Section 7.3.1.1:
  - Non-responders in the FAS
  - Responders in the FAS
  - Normofilterers in the FAS
  - All patients in the FAS
- An analysis of the primary endpoint on all patients in the FAS will be performed assuming that any treatment effect is linearly dependent upon randomisation baseline (visit 8) GFR. This will be performed using an adjusted MMRM model with an interaction term of treatment-by-baseline-GFR. The model will be fully specified in the TSAP.

  The gradient of the treatment effect, with confidence interval will be estimated. Estimates for the treatment effect will also be provided for certain randomisation baseline GFR values. These will be within the range of randomisation baseline values observed, at intervals of 15 mL/min/1.73m^2 and centred around the mean baseline value. 95% CIs will be provided for all estimates.
- The previous analysis of the primary endpoint will be repeated on all patients in the FAS using the MMRM model with linear dependence of treatment effect upon baseline GFR using screening baseline (visit 4) GFR.
- Treatment period 1 GFR response will be separately assessed by baseline-adjusted (randomisation, visit 8) ANCOVA for patients in the FAS for each of the following groups:
  - all patients
  - hyperfilterers
  - non-responders
  - responders
  - normofilterers.
- The natural logarithm of the primary endpoint will be analysed separately for hyperfilterers and all patients in the FAS. The MMRM model as described in Section 7.3.1.1 will be used with the modification that all GFR measurements (including baseline) will be replaced by their respective natural logarithms. Model outputs will be back-transformed and the estimate of the treatment effect reported as the ratio of GFR after empagliflozin and ramipril treatment divided by GFR on placebo and ramipril treatment, with 95% CI.
- Sensitivity analyses of the primary endpoint will be performed as follows:
  - The primary analysis for the primary endpoint, as detailed in Section 7.3.1.1, will be repeated for the hyperfilterers from the PPS.

- The primary analysis for the primary endpoint, as detailed in Section 7.3.1.1, will be repeated on hyperfilterers in the FAS, excluding patients who were prescribed at any time with < 10 mg ramipril during the double blinded treatment periods.
- The primary endpoint analysis for the primary endpoint, as detailed in Section 7.3.1.1, will be repeated using a fixed effect for patient.
- The primary endpoint analysis for the primary endpoint, as detailed in Section 7.3.1.1, will be repeated including sequence in the statistical model.

7.3.2 Secondary endpoint analyses

7.3.2.1 Primary Analysis

Filtration status, defined as whether GFR < 120 mL/min/1.73 m^2, after 4 weeks of treatment with placebo added to ramipril or treatment with empagliflozin added to ramipril (yes/no).

This will be analysed for the population of hyperfilterers in the FAS.

It will be statistically analysed by McNemar's test [R15-3496], with the odds ratio, 95 % CI and nominal p-value reported. It will also be descriptively analysed by the proportion with each status.

7.3.2.2 Secondary analyses

The following patient populations will be analysed using the same statistical methods as described for the primary analysis in Section 7.3.2.1:

- All patients in the FAS
- Non-responders in the FAS

In addition further analyses using different threshold values may be performed, to be defined in the TSAP.

7.3.4 Safety analyses

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

All treated patients will be included in the safety analysis and reporting will be by actual treatment at onset. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. The REP is defined as 7 days after the last dose of empagliflozin/placebo. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

AEs occurring prior to first intake of any trial medication will be assigned to 'screening'. AEs occurring from first pre-randomisation intake of ramipril until first intake of empagliflozin/placebo will be assigned to 'run-in'. AEs occurring while on empagliflozin/placebo or up to 7 days after intake will be assigned to the relevant double-blind treatment period. AEs occurring during the washout period and more than 7 days after intake of empagliflozin/placebo will be assigned to 'washout'. AEs occurring more than 7 days after final intake of empagliflozin/placebo in the second period will be assigned to 'post-study'. More details of the assignments, including the corresponding time intervals will be defined in detail in the TSAP.

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.

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

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

7.4 INTERIM ANALYSES

Although a DMC will review the safety data on an ongoing basis (see Section 3.1.1.4), no formal interim analysis is planned.

7.5 HANDLING OF MISSING DATA

Patients missing all post-randomisation GFR data are omitted from the FAS, as are those missing either or both the screening baseline (visit 4) and randomisation baseline (visit 8) GFR measurement.

For analyses by MMRM, missing response data will not be imputed: MMRM is a likelihood based method and as such can implicitly account for data that is Missing At Random (MAR). For analyses by McNemar's test, a missing binary response will not be imputed and will implicitly be treated by the analytical method as being the same as the patient's evaluable response for the other period.

For the ANCOVA analysis of period 1 only, patients missing a period 1 measurement will be excluded from the analysis. For the analysis of pre-randomisation GFR, patients missing either GFR measurement will be excluded. For all other further endpoints, patients missing both post-randomisation continuous measurements will be implicitly excluded by the MMRM method, while patients missing one or both binary measurements will also be omitted from analysis (implicitly treating the two measurements as being the same).

Methods to handle any other exceptional cases will be considered before unblinding the data and will be applied in a manner consistent with other trials of this type. The evaluability of patients with deviations from the protocol likely to confound the treatment response will be decided prior to unblinding.

7.6 RANDOMISATION

After measurement of baseline characteristics there will be an open-label run-in period of 4 weeks. The trial will then be performed as a double-blind design with respect to the two treatment sequences in the subsequent periods (ramipril+empagliflozin then ramipril+placebo and ramipril+placebo then ramipril+empagliflozin). Ramipril medication will be unblinded throughout as it does not vary between treatments.

At the end of the run-in period, patients will be randomised in blocks to the two study sequences in a 1:1 ratio. There will be no stratification at randomisation by GFR for logistical reasons.

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

7.7 DETERMINATION OF SAMPLE SIZE

In a previous study [R10-6368], it was found that the change in GFR from baseline after 8 weeks of treatment with ramipril in hyperfilterers was -34.9 mL/min/1.73m^2 (no CI specified, unadjusted for baseline). The mean baseline GFR for this sample was 177.7 mL/min/1.73m^2. In a separate study (ATIRMA, [c01802271-02]), it was found that the change in GFR from baseline after 8 weeks of treatment with empagliflozin monotherapy in hyperfilterers was -33.4 mL/min/1.73m^2 (95% CI: -46.2 to -20.6 mL/min/1.73m^2); this was also unadjusted for baseline and the mean baseline GFR for this sample was 172.2 mL/min/1.73 m^2. It is believed that response after 8 weeks treatment will be similar to response at 4 weeks.

The combination of ramipril and empagliflozin has not been investigated in clinical trials before so the extent of the additivity of their GFR reduction effects is unknown. Baseline GFR while on ramipril treatment (randomisation baseline) is likely to be considerably lower than before treatment (screening baseline):

From the ATIRMA trial, the effect of empagliflozin was found to be correlated with baseline GFR ($r = -0.78$, $r^2 = 0.60$). From all of this, it is therefore believed that an additional change in GFR from baseline of approximately -15 mL/min/1.73m^2 in hyperfilterers is likely for the combination treatment in comparison to the monotherapy.

In the same trial, the standard deviation of the change from baseline between individuals was found to be 35.3 mL/min/1.73m^2. However, this accounted for neither the strong negative correlation with baseline GFR, nor any correlations with other baseline characteristics that are inherently adjusted for in a cross-over trial by the use of within-subject comparisons.

For this crossover design, it is estimated that there is strong correlation between a subject's measurements of between $\rho = 0.68$ and 0.75. This is a reasonable range since r^2 between baseline and change from baseline was previously found to be 0.60, which does not account for any other baseline covariates. Total standard deviation (σ_T) may be related to within-subject standard deviation (σ_W) by the following formula:

$$\sigma_W = \sigma_T\sqrt{(1-\rho)}$$

Consequently, it is estimated that the intra-individual standard deviation is likely to be in the range of 17.5 to 20 ml/min/1.73m^2.

Under the assumptions of an effect size of -15 mL/min/1.73m^2, an intra-individual standard deviation of 17.5 mL/min/1.73m^2, a two-sided type I error rate of 0.05, and power of 90%, it was calculated that 16 hyperfilterer patients would be required per arm (i.e. treatment sequence) to demonstrate superiority, giving a total of 32 hyperfilterers. Including an additional 2 hyperfilterers to account for dropout, the minimum required sample size is 34 hyperfilterers.

As there is some uncertainty over the likely intra-individual standard deviation, Table 7.7:1 provides the power for a range of assumed standard deviations and effect sizes. From this, it can be seen that the trial is also reasonably-powered (82.7%) to detect the same effect size of -15 ml/min/1.73m^2 if the intra-individual standard deviation is 20.0 ml/min/1.73m^2, and has approximately 76% power to detect a smaller effect size of -12 ml/min/1.73m^2 if the intra-individual standard deviation is 17.5 mL/min/1.73m^2.

Table 7.7: 1 Power for a 2x2 crossover design with 16 hyperfilterers per arm under varying assumptions of effect size and intra-individual standard deviations. Calculations were performed using nQuery Advisor® 7.0 statistical package by Statistical Solutions Ltd.

	Intra-Individual Standard Deviation, ml/min/1.73m^2 (corresponding ρ)			
Effect Size mL/min/1.73m^2	**15.8 (0.80)**	**17.5 (0.75)**	**20.0 (0.68)**	**22.3 (0.60)**
-10	68.7%	59.9%	49.0%	41.1%
-12	83.6%	75.6%	64.1%	54.9%
-15	95.6%	**91.2%**	82.7%	74.0%
-18	>99.0%	97.8%	93.6%	87.7%

In summary, the sample size will be based upon the number of hyperfilterers, and will be a minimum of 34 hyperfilterers. The number of patients required to be randomised to provide this is expected to be approximately 74.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP, relevant BI Standard Operating Procedures (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 finalization of the Clinical Trial Report.

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 competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

(e)CRF 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 CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

Data should be transcribed into the eCRF based on the information contained within the 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. CRF/eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA / on site monitor and auditor may review all CRF / eCRF, 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 AE 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 IB (applicable Doc. No: c01678844-07). For the ramipril this is the Canadian Product Monograph. The current versions of these reference documents are to be provided in the ISF.

8.4.2 Expedited reporting of adverse events

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 END OF TRIAL

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

9. REFERENCES

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U12-2707-01 SCS appendix and integrated summary of safety 08 Feb 2013

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		26 Apr2016
EudraCT number		NA
BI Trial number		1245.100
BI Investigational Product(s)		Empagliflozin
Title of protocol		A double-blind, placebo controlled, cross-over renal mechanistic trial to assess the effect of adding empagliflozin versus placebo on renal hyperfiltration in patients with type 1 diabetes on a background of the angiotensin converting enzyme inhibitor (ACEi) ramipril: BETWEEN Study
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	X	
Section to be changed		Flow Chart
Description of change		"X" removed for the collection of biomarker samples being collected at the follow-up visit.
Rationale for change		To make the flow chart consistent with section 5.5.
Section to be changed		Flow Chart
Description of change		"X" added to ECG at the follow-up visit.
Rationale for change		To make the flow chart consistent with section 5.3.4.
Section to be changed		Foot notes to the flow chart
Description of change		Foot note 2 was revised to indicate that 3 sets of BP measurements would be collected at routine clinic visits. "Postural vitals" was removed.
Rationale for change		To make the flow chart foot notes consistent with section 5.2.4.1 and 5.2.4.2.

Section to be changed		Foot notes to flow chart
Description of change		Foot note 14 was updated to reflect administration of study medication in the morning and that the arterial stiffness, NICOM, SNS measurements and lab samples (renal panel) will be collected prior to sample collect for inulin and PAH. Per table 5.3.3:1 footnote 1, BHB sample collecting times were included.
Rationale for change		To make the foot note instructions consistent with other sections of the protocol (section 4.1.4, 5.3.3).
Section to be changed		3.1
Description of change		Assessment day -29 was changed to -28
Rationale for change		To make the day for the renal assessments consistent with the flow chart.
Section to be changed		4.1.1
Description of change		Added Valeant Pharmaceuticals as another source of ramipril.
Rationale for change		Ramipril re-supply medication was purchased from as was no longer supplying ramipril in
Section to be changed		4.1.4
Description of change		Correct the study day that Ramipril is started.
Rationale for change		To make this section consistent with the flow chart.
Section to be changed		4.2.1
Description of change		Guidance is provided for insulin reductions when starting blinded study medication. It was clarified that daily ketone monitoring should occur prior to breakfast.
Rationale for change		Clarification / optimisation of suggested insulin titration and alignment with phase III trials.
Section to be changed		4.2.2.2
Description of change		Correct the day when the modified diet should be started and to correct the last study visit number.
Rationale for change		To make this section consistent with the flow chart.
Section to be changed		
Description of change		

Rationale for change		
Section to be changed		5.2.4.2
Description of change		Reference to postural blood pressure was removed.
Rationale for change		Postural vitals could be mis-interpreted as 'orthostatic' blood pressure which is not required for this trial. Routine BP measurements will be taken consistently throughout the study following the procedure outlined in section 5.2.4.1.
Section to be changed		5.3.5.2
Description of change		It was clarified that all hypoglycaemias will not be reported in the eCRF but they will be documented.
Rationale for change		To ensure consistency with reporting in other trials.
Section to be changed		5.3.6.1
Description of change		The section for "always serious AEs" was updated to describe the list of AEs as a list of further AEs.
Rationale for change		To make the section consistent with the current version of the CTP template.
Section to be changed		7.3
Description of change		Names of analysis sets were revised.
Rationale for change		To make the names of the analysis sets consistent with project standards.
Section to be changed		7.3.1.1
Description of change		Modification of the description of the REML and Kenward Roger methods being used.
Rationale for change		To clarify the effect of the methods specified.
Section to be changed		7.3.1.2
Description of change		Modification of pre-specified output from secondary analyses based upon the treatment-by-baseline interaction model. Change of criteria for sensitivity analysis excluding <10 mg ramipril dose patients from treated to prescribed.

Rationale for change		Outputs as specified were insufficiently different from estimates of treatment effect at given baseline values already being calculated. Criteria for dose assignment aligned with other analyses.
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		8.4.1
Description of change		The document used for listedness for Ramipril was changed from the SmPC to the Canadian Product Monograph.
Rationale for change		Since this was a single centre study that is being conducted in Canada, the Canadian label would be used for assessing listedness.
Section to be changed		8.4.2
Description of change		BI is the responsible party for expedited reporting of AEs.
Rationale for change		To clarify the reporting responsibilities.

Number of global amendment		2.0
Date of CTP revision		22 Sep 2016
EudraCT number		NA
BI Trial number		1245.100
BI Investigational Product(s)		Empagliflozin
Title of protocol		A double-blind, placebo controlled, cross-over renal mechanistic trial to assess the effect of adding empagliflozin versus placebo on renal hyperfiltration in patients with type 1 diabetes on a background of the angiotensin converting enzyme inhibitor (ACEi) ramipril: BETWEEN Study
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		Synposis – Main criteria for inclusion
Description of change		Changed Hb_{A1c} lower limit from 7% to 6.5%.
Rationale for change		To reduce the number of patients, who are otherwise suitable, but screen fail due to an Hb_{A1c} value that is just below 7%.
Section to be changed		2.3 Benefit – Risk Assessment
Description of change		Investigators should differentiate deteriorating ketosis / DKA from any milder ketone values.
Rationale for change		To provide guidance on safety monitoring.
Section to be changed		3.3 Description of Trial Population
Description of change		Instructions on re-screening patients has been included.
Rationale for change		To permit re-screening of patients who have screen failed but could be re-screened if the patient was considered to be a good potential candidate for the trial.
Section to be changed		3.3.2 Inclusion criteria #4

Description of change		Hb_{A1c} value was changed from 7% to 6.5%
Rationale for change		To reduce the number of patients, who are otherwise suitable, but screen fail due to an Hb_{A1c} value that is just below 7%.
Section to be changed		3.3.2 Inclusion criteria # 10
Description of change		Removed tubal occlusion as a method of surgical sterilization per ICH M3 (R2) guidance.
Rationale for change		Tubal ligation is considered to be a highly effective method of contraception and no longer a method of permanent sterilisation
Section to be changed		3.3.3 Exclusion criteria #4
Description of change		Severe hypoglycaemia involving unconsciousness was added.
Rationale for change		Adjustment of eligibility for safety reasons and for clarification.
Section to be changed		4.2.2.2 Restrictions on diet and lifestyle
Description of change		Extreme diets such as the ketogenic diet are prohibited during the trial.
Rationale for change		Add for clarification of patient safety.
Section to be changed		5.2.1 Haemodynamic measurements
Description of change		Included measurement of haematocrit every 30 min once equilibrium has been achieved.
Rationale for change		Omitted in error from previous version of protocol
Section to be changed		5.2.2 Segmental tubular handling of sodium
Description of change		Blood and urine samples will be collected at 3 time-points. Types of samples collected are included.
Rationale for change		Clarification of sample collection.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Removed statement that re-screening is not permitted.
Rationale for change		Re-screening will be permitted in the study.
Section to be changed		Various sections
Description of change		IB reference number has been changed from c01838761 to c01678844-07
Rationale for change		Updated IB version was assigned a different document number.

Number of global amendment		3.0
Date of CTP revision		03 Jul 2018
EudraCT number		NA
BI Trial number		1245.100
BI Investigational Product(s)		Empagliflozin
Title of protocol		A double-blind, placebo controlled, cross-over renal mechanistic trial to assess the effect of adding empagliflozin versus placebo on renal hyperfiltration on a background of the angiotensin converting enzyme inhibitor (ACEi) ramipril: BETWEEN Study
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		Title Page
Description of change		Reference to type 1 diabetes patients was removed from the protocol title.
Rationale for change		The trial is proposed to recruit patients who have type 1 diabetes, type 2 diabetes or are obese. Therefore a strict reference to type 1 patients was removed to reflect revision to the protocol entry criteria.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Reference to type 1 diabetes patients was removed from the protocol title and objectives.
Rationale for change		The trial is proposed to recruit patients who have type 1 diabetes, type 2 diabetes or are obese. Therefore a strict reference to type 1 patients was removed to reflect revision to the protocol entry criteria.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Planned number of patients changed from 62 to 74

		with 37 patients in each treatment group.
Rationale for change		Number of patients adjusted according to sample size re-calculation.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Type 2 diabetes and obesity is added to the diagnosis and main inclusion criteria. Abbreviations for type 1 diabetes and type 2 diabetes were added.
Rationale for change		The trial is proposed to recruit patients who have type 1 diabetes, type 2 diabetes or are obese. Therefore diagnosis and main inclusion criteria is updated accordingly.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Duration for screening period lengthened from 2 weeks to 4 weeks.
Rationale for change		To permit possible wash-out of RAAS inhibitors which may be safely discontinued.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Updated definition of filtration status is defined as GFR < 120 ml/min/1.73m^2.
Rationale for change		The primary efficacy subgroup of patients has changed from non-responders to hyperfilterers, GFR filtration status threshold value lowered as lower baseline GFR values expected in this subgroup.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		The primary analysis will be conducted in patients who have a GFR ≥ 135 ml/min/1.73m^2 at visit 4 rather than at visit 8.
Rationale for change		ACE-I non-responder analysis will be a sub-group analysis rather than the primary analysis.
Section to be changed		Flow Chart
Description of change		Visit windows were adjusted during the screening period to permit for additional time to allow wash-out of RAAS inhibitors and to obtain GFR results from visit 4.
Rationale for change		Patients should not be taking a RAAs inhibitor while taking study treatment. Patients who can safety discontinue the prescribed RAAS inhibitor may undergo a 2 week wash-out prior to starting visit 2. GFR from visit 4 must be known prior to

		proceeding with visit 4a.
Section to be changed		Flow Chart
Description of change		Introduction of a wash-out for patients taking an existing RAAS inhibitor.
Rationale for change		Patients should not be taking a RAAs inhibitor while taking study treatment. Patients who can safety discontinue the prescribed RAAS inhibitor may undergo a 2 week wash-out prior to starting visit 2.
Section to be changed		Flow Chart
Description of change		Visit 4 has been split into two separate visits called visit 4 and visit 4a. Visit 4a includes dispensing and administration of ramipril, collection of AEs and changes in concomitant therapies.
Rationale for change		Approximately 10 patients with normofiltration will be included after the approval of the amendment. Filtration status from visit 4 must be known prior to initiating ramipril therapy.
Section to be changed		Flow Chart Footnotes
Description of change		Footnote 5: clarified that ketones will only be monitored in patients with T1D or patients whose diabetes is managed solely with insulin.
Rationale for change		Patients who are at higher risk for KA are required to monitor blood ketones whilst participating in the trial.
Section to be changed		Flow Chart Footnotes
Description of change		Footnote 9: Self home blood glucose monitoring is only required in patients with diabetes. Frequency of testing for patients with T1D and T2D is clarified.
Rationale for change		Obese patients who do not have diabetes are not required to monitor their blood sugars unless deemed necessary by the investigator.
Section to be changed		Flow Chart Footnotes
Description of change		Footnote 14: Obese patients may not require a euglycaemic clamp, based on investigator judgment. If a patient does not require the euglycemic clamp, the timing the procedures will be maintained per protocol.
Rationale for change		Obese patients who are euglycaemic do not require a clamp as their blood glucose will be between 4-6

		mmol/L.
Section to be changed		Flow Chart Footnotes:
Description of change		Assessment tables were updated to reflect the protocol for inulin infusion and iohexol infusion.
Rationale for change		Iohexol will be utilized to measure GFR after amendment 4 due to availability of inulin.
Section to be changed		Flow Chart Footnotes
Description of change		Footnote 15: reference to euglycaemic clamp was removed and replaced with the specific visit numbers.
Rationale for change		Not all patients will require a euglycaemic clamp. Visits are identified based on visit number.
Section to be changed		Flow Chart Footnotes
Description of change		Footnote 17: clarified that ramipril will be administered at visit 4a.
Rationale for change		Due to the split in visit 4 procedures, the ramipril will be administered and dispensed at visit 4a.
Section to be changed		Flow Chart Footnotes
Description of change		Footnote 20: new footnote added to explain requirements for conducting visit 4a.
Rationale for change		GFR values need to be reviewed to ensure that hyperfilterer patients are included in the study.
Section to be changed		Flow Chart Footnotes
Description of change		Footnote 21: new footnote added to explain the wash-out requirement for patients taking a RAAS inhibitor.
Rationale for change		Patients should not be taking a RAAs inhibitor while taking study treatment. Patients who can safety discontinue the prescribed RAAS inhibitor may undergo a 2 week wash-out prior to starting visit 2.
Section to be changed		Abbreviations
Description of change		Added abbreviations for chronic kidney disease and end stage renal disease. Removed abbreviations for type 1 diabetes hyperfilterer, type 1 diabetes normofilterer and remote data capture.
Rationale for change		Abbreviations updated based on usage in the protocol amendment document.

Section to be changed		1.1 Medical Background
Description of change		Removed reference to prevalence and management of T1D.
Rationale for change		Study population is expanded to include additional patient groups including T2D and obese patients.
Section to be changed		1.1 Medical Background
Description of change		Included medical rationale for inclusion of obese patients.
Rationale for change		Medical rationale for inclusion of obese patients is required.
Section to be changed		1.2.2.1 Clinical pharmacokinetics – type 2 diabetes mellitus
Description of change		PK of empagliflozin in healthy volunteers was added.
Rationale for change		Obese patients may not have diabetes and therefore PK of empagliflozin in non-diabetic patients is relevant.
Section to be changed		2.1 Rationale for Performing the Study
Description of change		Included rationale for inclusion of obese patients.
Rationale for change		Nephropathy may be caused by several factors including diabetes as well as obesity.
Section to be changed		2.1 Rationale for Performing the Study
Description of change		Removed reference inclusion of patients who are ACEi non-responders and that conditions of euglycaemia may not be controlled.
Rationale for change		Study analysis was broadened to analyse patients who are hyperfilterers. Euglycaemic patients may not require a euglycaemic clamp.
Section to be changed		2.2 Trial Objectives
Description of change		References to patients with T1D and controlled euglycaemia were removed.
Rationale for change		Additional patient groups (T2D and obese patients) may be enrolled. Euglycaemic patients may not require a euglycaemic clamp.
Section to be changed		2.3 Benefit-risk assessment
Description of change		Added information related to the potential risk for inclusion of non-diabetic (euglycaemic) patients in the study.
Rationale for change		Additional patient groups (T2D and obese patients)

		may be enrolled and risk needs to be assessed.
Section to be changed		2.3 Benefit-risk assessment
Description of change		Removed references to T1D-N and T1D-H.
Rationale for change		Additional patient groups (T2D and obese patients) may be enrolled.
Section to be changed		3.1 Overall trial design and plan
Description of change		References to controlled euglycaemia were removed.
Rationale for change		Euglycaemic clamp is not required for patients who are euglycaemic.
Section to be changed		Figure 3.1:1 Trial Design
Description of change		Figure updated to reflect revised visit structure.
Rationale for change		Figure of trial design should reflect the required procedures and visits in the protocol.
Section to be changed		3.2 Discussion of Trial Design, Including the Choice of Control Group(s)
Description of change		References to type 1 diabetes patients was removed.
Rationale for change		Additional patient groups (T2D and obese patients) may be enrolled.
Section to be changed		3.2 Discussion of Trial Design, Including the Choice of Control Group(s)
Description of change		The starting dose of ramipril is recommended to be 5 mg followed by an up titration rather than indicating that the starting dose will be 5 mg.
Rationale for change		To permit the investigator to prescribe a lower dose of ramipril based on clinical judgment.
Section to be changed		3.2 Discussion of Trial Design, Including the Choice of Control Group(s)
Description of change		Removed reference to hyperfilterer T1D patients.
Rationale for change		Additional patient groups (T2D and obese patients) may be enrolled.
Section to be changed		3.2 Discussion of Trial Design, Including the Choice of Control Group(s)
Description of change		Revised the GFR range for normofiltering patients from 90-134 ml/min/1.73m^{2}to 60 to 134 ml/min/1.73m^2.
Rationale for change		Correction made to the range since the entry

		criteria would allow patients to be entered if the eGFR ≥ 60 ml/min/1.73m^2 based on creatinine measured by the central laboratory at Visit 1
Section to be changed		3.3 Selection of Trial Population
Description of change		Updated the planned number of screened and randomized patients from 75 screened patients to 150 screened patients and 62 randomized patients was revised to 74 randomized patients.
Rationale for change		It was determined based on sample size recalculation that approximately 74 patients will be required. Based on prior experience screening for patients with hyperfiltration, additional patients will need to be screened to achieve 74 randomized patients.
Section to be changed		3.3 Selection of Trial Population
Description of change		Enrolment of additional patients with normofiltration is capped such that only 40 normofilterer patients may be randomized into the trial. Screening will continue until the required number of hyperfilterer patients are randomized into the trial.
Rationale for change		To ensure that the patient population of interest (hyperfilterer patients) are randomized into the trial.
Section to be changed		3.3 Selection of Trial Population
Description of change		Changed remote data capture (RDC) to electronic data capture (eDC) system.
Rationale for change		The RDC system will no longer be used for data capture from site.
Section to be changed		3.3.1 Main Diagnosis for Trial Entry
Description of change		The main diagnosis for trial entry was revised to include patients with type 2 diabetes and obese patients.
Rationale for change		Nephropathy may be caused by several factors including diabetes as well as obesity.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inclusion criteria #2 was revised to permit the enrolment of patient with type 2 diabetes or non-diabetic obese patients into the trial.
Rationale for change		Nephropathy may be caused by several factors including diabetes as well as obesity.

Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inclusion criteria #3 was clarified to indicate that type 1 diabetic patients must either use MDI or CSII.
Rationale for change		It is expected that only patients with type 1 diabetes will utilized insulin therapy to manage their diabetes.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inclusion criteria #4 was clarified to indicate that the HbA1c criteria is relevant for patients with either type 1 diabetes or type 2 diabetes.
Rationale for change		It is not expected that non-diabetic obese patients will have an HbA1c of 6.5%.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inclusion criteria #5 was clarified to indicate that type 1 diabetic patients must have a good understanding of their disease.
Rationale for change		Type 1 diabetic patients must have a good understanding of their disease and how to manage diabetes as a risk mitigation strategy.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inclusion #7, body mass index was revised to remove the upper restriction (35 kg/m^2).
Rationale for change		Obese patients may have a BMI> 35 kg/m^2.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		The footnote that defines women of child bearing potential appeared twice. The duplicate wording was removed.
Rationale for change		Duplicate information is redundant.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Exclusion criteria #1 was revised to indicate that type 1 diabetic patients should not be treated with antihyperglycaemic agents other than insulin.
Rationale for change		Type 2 diabetic patients may be treated with antihyperglycaemic agents (except SGLT2 inhibitors as indicated in exclusion criteria #2).
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Exclusion criteria #10 was revised to exclude

		patients who required RAAS inhibitors.
Rationale for change		Study will permit patients to undergo a wash-out of RAAS inhibitors.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Exclusion criteria #13 was revised to exclude patients who had surgical treatment for weight loss or aggressive diet and was clarified that patients with type 1 diabetes should not use anti-obesity drugs within 3 months prior to visit 1.
Rationale for change		Some obese patients may use anti-obesity medications.
Section to be changed		4.1.3 Selection of Doses in the Trial
Description of change		Clarified that ramipril treatment should be initiated with a starting dose of 5 mg and the dose of 7.5 mg q.d. may be provided if this is the maximum tolerated dose for a patient.
Rationale for change		Permit the investigator to dose-adjust the ramipril therapy so that patients are on maximum tolerated dose.
Section to be changed		Table 4.1.4:1 Oral administration of study medications per dose group
Description of change		The week number for the run-in period was removed.
Rationale for change		To ensure consistency with the flow chart.
Section to be changed		4.1.4 Drug Assignment and Administration of Doses for each Patient
Description of change		Ramipril will first be dispensed at visit 4a rather than at visit 4. The administration of the first dose of ramipril should occur at the clinic.
Rationale for change		To ensure consistency with the flow chart.
Section to be changed		4.2.1 Rescue Medication, Emergency Procedures, and Additional Treatment(s)
Description of change		Clarified that no anti-hyperglycaemic agents, including insulin will be provided as part of the study supplies.
Rationale for change		Type 2 diabetic patients may take other anti-hyperglycaemic agents other than insulin.
Section to be changed		4.2.1 Rescue Medication, Emergency Procedures, and Additional Treatment(s)
Description of change		Clarified that management of hypoglycaemia

		should be done in all patients with diabetes.
Rationale for change		Type 2 diabetic patients are eligible to participate under the amendment.
Section to be changed		4.2.1 Rescue Medication, Emergency Procedures, and Additional Treatment(s)
Description of change		Clarified that dose adjustment in total insulin dose should be performed according to the patient HbA1c in patients with type 1 diabetes. Clarified that ketone monitoring is required for patients who are insulin dependent (T1D and T2D).
Rationale for change		Insulin dose adjustment is relevant for patients with type 1 diabetes and ketone monitoring is also relevant for T2D patients.
Section to be changed		4.2.1 Rescue Medication, Emergency Procedures, and Additional Treatment(s)
Description of change		Patients with type 1 diabetes need to have a good understanding on how to manage their disease.
Rationale for change		Consistency with protocol inclusion criteria #5.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Clarified that patients with type 1 diabetes should not take antihyperglycaemic agents other than insulin.
Rationale for change		Patients with type 1 diabetes must be treated in accordance with approved therapies.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Patients should not take another SGLT2-inhibitor during the trial including the follow-up period.
Rationale for change		Patients should not take a prescribed SGLT2 inhibitor since patients will receive empagliflozin during one of the two dosing periods.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Patients with type 1 diabetes are prohibited from taking anti-obesity medications or systemic steroids.
Rationale for change		Due to potential increased risk of taking medications that may impact metabolism in patients with type 1 diabetes.

Section to be changed		4.2.2.2 Restrictions on diet and lifestyle
Description of change		Revised the days when renal study visits will occur.
Rationale for change		To ensure consistency with the updated flow chart.
Section to be changed		5.1.2 Secondary Endpoint
Description of change		Revised the definition of filtration status to 120 ml/min/1.73m^2).
Rationale for change		The primary efficacy subgroup of patients has changed from non-responders to hyperfilterers, GFR filtration status threshold value lowered as lower baseline GFR values expected in this subgroup.
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		5.2.1 Hemodynamic measurements
Description of change		Clarified that in all patients blood glucose will be routinely monitored to ensure that plasma glucose is between 4-6 mmol/L. A modified clamp technique may be used, if required, to maintain blood glucose in patients with elevated blood sugars and in all patients with diabetes.
Rationale for change		Obese patients who are euglycaemic do not require the invasive clamp technique.
Section to be changed		5.2.1 Hemodynamic measurements
Description of change		Clarified that in the first 31 randomized patients into the trial inulin will be used to measure GFR. However in all remaining patients iohexol will be used to measure GFR. Timing of iohexol infusion and blood sample collection as added to the protocol.
Rationale for change		Based on the availability of inulin.
Section to be changed		5.3.2.1 Self Blood Glucose Monitoring
Description of change		Clarified that all patients with diabetes will be provided with SBGM equipment. Frequency of

		testing was defined for patients with type 2 diabetes.
Rationale for change		Study will permit the enrolment of patients with type 2 diabetes. SBGM will need to be performed in these patients in accordance with clinical practice guidelines or as recommended by the investigator.
Section to be changed		5.3.2.2 Ketone Monitoring
Description of change		Ketone monitoring is required in patients with T1D and patients who are only using insulin for their management of diabetes. Patients who are managing type 2 diabetes with oral anti-hyperglycaemic agents do not need to monitor ketones, unless deemed necessary by the investigator.
Rationale for change		Patients who manage their diabetes solely with insulin are at higher risk of KA and therefore need to monitor their ketones routinely.
Section to be changed		Table 5.3.3:1 Safety Laboratory Parameters
Description of change		Clarified that C peptide will be performed in type 1 diabetic patients only.
Rationale for change		Only relevant in type 1 diabetic patients.
Section to be changed		5.3.3. Safety laboratory parameters
Description of change		Clarified laboratory parameters to be performed at visit 1. Clarified that prescribed medications should be taken as instructed by the prescribing physician.
Rationale for change		Protocol clarification.
Section to be changed		5.3.3. Safety laboratory parameters
Description of change		Inulin and PAH will be analysed by the local lab however removed statement that all labs will be conducted by the central lab.
Rationale for change		All lab assessments that are tested by the central lab will be included in the lab specification document.
Section to be changed		5.3.6.1 Definitions of adverse events
Description of change		Changed remote data capture (RDC) to electronic data capture (eDC) system.
Rationale for change		The RDC system will no longer be used for data capture from site.

Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Clarified that screening procedures may be performed over several days within the screening window.
Rationale for change		Protocol clarification.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Added information on RAAS wash-out.
Rationale for change		Patients who are taking a RAAS inhibitor and who can safety discontinue therapy may under a wash-out.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Patients with type 1 diabetes as well as patients who manage their diabetes with inulin should be provided with a glucose / ketone meter.
Rationale for change		Risk mitigation strategy for potential KA.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Patients should not receive their run-in medication until after the GFR results from visit 4 are known. Run-in will need to be based on the patients screening GFR value.
Rationale for change		To ensure that the required number of hyperfilterer patients are entered into the trial.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Clarified that at visit 4a, site staff should obtain the ramipril kit number via the IRT system.
Rationale for change		To ensure consistency with the flow chart.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		GFR that is measured at visit 8 will be monitored to ensure that a sufficient number of patients with renal hyperfiltration are included into the study.
Rationale for change		To ensure that there are a sufficient number of patients with renal hyperfiltration to conduct the analysis.
Section to be changed		6.2.2.4 Unscheduled visits during the treatment period
Description of change		For patients requiring a dose adjustment to their ramipril therapy, the dose of 7.5 mg q.d. or 5 mg b.i.d. is recommended.
Rationale for change		Patients should take either 10 mg ramipril or

		maximum tolerated dose.
Section to be changed		7.1 Statistical Design - Model
Description of change		Added patients with type 2 diabetes or obesity. GFR will be assessed under euglycaemic conditions.
Rationale for change		Patients with type 2 diabetes and obesity are at risk for development of nephropathy. Therefore these patients will also be assessed in the study. GFR measurements will be performed under euglycaemic condition however a euglycaemic clamp may not be required in obese patients who do not have diabetes.
Section to be changed		7.1 Statistical Design - Model
Description of change		Ordering of subgroups was revised to list hyperfilterer patients first.
Rationale for change		Main analysis will be performed on patients who have renal hyperfiltration at visit 4.
Section to be changed		7.1 Statistical Design - Model
Description of change		Clarified that non-responders and responders are sub-groups of hyperfilterers.
Rationale for change		Protocol clarification.
Section to be changed		7.2 Null and alternative hypothesis
Description of change		Population of interest will be patients with renal hyperfiltration.
Rationale for change		Due to challenges with identifying patients with renal hyperfiltration who are also non-responders to ACE inhibition.
Section to be changed		7.3.1.1 Primary analysis
Description of change		Primary analysis will be performed on the hyperfilterer sub-group (based on visit 4 GFR) rather than the non-responder sub-group (based on visit 8 GFR).
Rationale for change		Due to challenges with identifying patients with renal hyperfiltration who are also non-responders to ACE inhibition.
Section to be changed		7.3.1.2 Secondary and sensitivity analysis
Description of change		A sensitivity analysis will be performed in the non-responder sub-group.
Rationale for change		Primary analysis was will be performed on the hyperfilterer sub-group.

Section to be changed		7.3.1.2 Secondary and sensitivity analysis
Description of change		The gradient of the treatment effect will be calculated based on randomization baseline GFR values that are centred around the mean baseline value.
Rationale for change		Due to challenges with identifying patients with renal hyperfiltration who are also non-responders to ACE inhibition, a baseline value of 135 ml/min/1.73m^2 no longer expected to be a central value.
Section to be changed		7.3.1.2 Secondary and sensitivity analysis
Description of change		Primary endpoint will be analysed separately for hyperfilterer patients.
Rationale for change		Consistency with section 7.3.1.1
Section to be changed		7.3.2.1 Primary analysis
Description of change		Definition of filtration status was re-defined as 120 ml/min/1.73m^2 in patients treated with placebo added to ramipril or empagliflozin added to ramipril.
Rationale for change		The primary efficacy subgroup of patients has changed from non-responders to hyperfilterers, GFR filtration status threshold value lowered as lower baseline GFR values expected in this subgroup.
Section to be changed		7.3.2.2 Secondary analysis
Description of change		Secondary analysis will be performed in the non-responder sub-group with further analysis defined in the TSAP.
Rationale for change		Primary analysis will be based on the hyperfilterer subgroup.
Section to be changed		7.5 Handling of missing data
Description of change		Patients missing the visit 4 GFR will be omitted from the FAS.
Rationale for change		Visit 4 GFR is required to determine if the patient is a hyperfilterer.
Section to be changed		7.7 Determination of sample size
Description of change		Details of the effect size from the ATIRMA trial were removed.
Rationale for change		No longer applicable due to the change in the primary efficacy subgroup of interest.

Section to be changed		7.7 Determination of sample size
Description of change		Effect size was assumed to be -15 ml/min/1.73m^2
Rationale for change		Study now powered to detect a smaller treatment effect that is still considered to be clinically meaningful.
Section to be changed		7.7 Determination of sample size
Description of change		Sample size was re-calculated based of the hyperfilterer patient population and estimated that 34 hyperfilterer patients are required.
Rationale for change		Due to challenges with identifying patients with renal hyperfiltration who are also non-responders to ACE inhibition.
Section to be changed		9.1 Published references
Description of change		The following published reference were added: P16-01830, R04-2173, P16-06807, R09-2151, R18-1327, R18-1328, R18-1329, R18-1330, R18-1807 and R18-1808. The following reference was removed from section 9.1: R09-2151.
Rationale for change		References were required for the updates made to the medical background and benefit-risk assessment sections of the protocol amendment.
Section to be changed		9.2 Unpublished references
Description of change		The following unpublished references were added: U12-2707-01 and c11963611-01.
Rationale for change		References were required for the updates made to the benefit risk assessment section of the protocol amendment.

APPROVAL / SIGNATURE PAGE

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Title: A double-blind, placebo controlled, cross-over renal mechanistic trial to assess the effect of adding empagliflozin versus placebo on renal hyperfiltration on a background of the angiotensin converting enzyme inhibitor (ACEi) ramipril: BETWEEN Study

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor		04 Jul 2018 14:46 CEST
Author-Trial Statistician		04 Jul 2018 15:12 CEST
Approval-Team Member Medicine		04 Jul 2018 16:05 CEST
Approval-Therapeutic Area		06 Jul 2018 10:11 CEST
Verification-Paper Signature Completion		06 Jul 2018 13:52 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed