Trial Protocol

REnal and **C**ardiovascular **E**ffects of SGLT2 inhibition in combination with loop **D**iur**E**tics in diabetic participants with **C**hronic **H**eart **F**ailure.

Trial Acronym	RECEDE-CHF
Sponsor	University of Dundee-NHS Tayside
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PROTOCOL APPROVAL

REnal and **C**ardiovascular **E**ffects of SGLT2 inhibition in combination with loop **D**iur**E**tics in diabetic patients with **C**hronic **H**eart **F**ailure. (RECEDE-CHF)

EudraCT number **2016-003968-39**

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above trial.

Professor Chim Lang		
Chief Investigator	Signature	Date
Dr Natalie Mordi		
Individual Responsible for Statistical Review	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CHF	Chronic Heart Failure
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRC	Clinical Research Centre
CRF	Case Report Form
CTIMP	Clinical Trials of Investigational Medicinal Product
DM	Diabetes Mellitus
DPPIV	Dipeptidyl peptidase inhibitor
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FBC	Full Blood Count
GCP	Good Clinical Practice
GP	General Practitioner
HbA1c	Glycated Haemoglobin
HF	Heart Failure
HIC	Health Informatics Centre
HR	Heart Rate
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LFTs	Liver Function Tests
LPLV	Last Participant Last Visit
LVSD	Left Ventricular Systolic Dysfunction
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
NYHA	New York Heart Association
PI	Principal Investigator
PSF	Pharmacy Site File
QC	Quality Control
R&D	Research & Development
REC	Research Ethics Committee
RPT	Renal Physiological Test
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDRN	Scottish Diabetes Research Network
SGLT2	Sodium-Glucose co-Transporter-2
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

SU	Sulphonylureas
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2D	Type 2 Diabetes
TASC	Tayside Medical Sciences Centre
TCTU	Tayside Clinical Trials Unit
TG	Tubulo-glomerular
TMF	Trial Master File
U&Es	Urea & Electrolytes
UAR	Unexpected Adverse Reaction
UoD	University of Dundee

SUMMARY

Lay Summary

People with diabetes are at increased risk of developing Heart Failure (HF). Symptoms of HF include increased shortness of breath, reduced ability to exercise and in some cases premature death as the heart becomes less efficient at pumping blood around the body. Many of these symptoms are caused by fluid retention.

Drug options to treat HF in diabetes are currently limited as many of the drugs used are not suitable in diabetic participants as they cause unpleasant or harmful side effects. Many participants are given water tablets to help reduce or prevent fluid retention.

A new class of anti-diabetic drugs may have some benefit in HF with diabetes as they may reduce workload on the heart. It has been shown that they may also promote weight loss and increase exercise capacity in previous studies.

This trial will test if there is any benefit from using a drug called empagliflozin, (an SGLT2 inhibitor), to boost the effects of water tablets in diabetic participants with heart failure, by increasing sodium and urine output.

The findings of this trial may help to find out if this class of drugs, SGLT2 inhibitors, are useful in diabetic participants with HF.

In this trial, the aim is to recruit participants who have diabetes and heart failure. Participants will undergo investigations of kidney function, renal physiological tests, by measuring urine and sodium excretion.

As this is a two-way cross over clinical trial, participants will be randomly allocated to either empagliflozin 25mg (6 weeks) or a dummy medication (placebo) (6 weeks), with a two week wash-out period between each arm. This will allow the researchers to compare if there is a difference between normal treatment and the addition of empagliflozin. Participants will undergo renal physiological testing at the end of week 1 and week 6 during each arm. Participants will continue as normal with currently prescribed medication for their diabetes and heart failure.

Professional Summary

Men and women with diabetes have a 2-5 fold increased risk of heart failure (HF). The prevalence and incidence of HF is increasing in diabetes and mortality rates remain alarmingly high. This highlights the need for novel therapies in diabetes that will reduce HF risk and/or delay disease progression.

Type 2 Diabetes Mellitus (T2DM) and Chronic Heart Failure (CHF) is a common but lethal combination where therapeutic options are limited.

In CHF loop diuretics are a mainstay of therapy and are required to treat fluid retention. However, following their chronic use many people develop diuretic resistance leading to a worsening of CHF. Combining thiazide-like diuretics with loop diuretics is a commonly used but ineffective strategy to overcome diuretic resistance. Thus, new treatment strategies are urgently needed.

SLGT2 inhibitors, the newest class of anti-diabetic drugs, may have additional beneficial cardio-renal effects in participants with concomitant DM and CHF. SGLT2 inhibitors have an osmotic diuretic effect by reducing sodium and glucose absorption in the proximal tubules of the nephrons. We hypothesize that these effects could potentially be beneficial in treatment of participants with HF who are prone to sodium and fluid retention.

The aim of this trial is to assess the safety and efficacy of empagliflozin, an SGLT2 inhibitor, when prescribed in participants with DM and CHF who are on loop diuretics. We will conduct a double-blind, randomised controlled crossover trial of 34 participants with DM and stable CHF who are on furosemide. Participants will be randomised to either empagliflozin 25mg once daily or placebo for six weeks before crossing over to receive either placebo or empagliflozin for a further six weeks (after a 2 week washout period).

Participants will undergo detailed renal physiological assessment after 1 week of treatment and end of each treatment period to assess renal physiological parameters to ascertain whether the addition of empagliflozin in conjunction with an intravenous bolus of furosemide improves urine output without any significant adverse consequences. The primary endpoint of the trial is a change in urinary volume in response to furosemide with empagliflozin when compared to placebo.

If our hypothesis is confirmed, it may position SGLT2 inhibitors such as empagliflozin as a mainstay of treatment in participants with DM and CHF. Additionally, it may help to provide an understanding of some of the mechanisms that may provide an improvement in cardiovascular outcome with SGLT2 inhibitors shown in the recently published EMPA-REG[15] trial.

1 INTRODUCTION

1.1 BACKGROUND

Chronic heart failure (CHF) and type 2 diabetes (T2D) frequently coexist. In population based studies and in CHF trials, the prevalence of T2D among participants with symptomatic heart failure (HF) is estimated to be between 12% and 41%.[1] Among all participants hospitalised for CHF, it has been reported that up to 40% have T2D.[2, 3] This association can be lethal since T2D has consistently been shown to be an independent predictor of increased morbidity and mortality in participants with CHF.[4] However, treating participants with concomitant HF and T2D can be challenging. In the treatment of T2D, European Association for the Study of Diabetes/American Diabetes Association guidelines recommend tailoring therapeutic approaches to individual needs and/or risks.[5] For most participants, metformin is the first choice anti-diabetic drug in all T2D participants including those with coincidental HF.[6] This is underpinned by observational population cohort studies including our own observation in the Scottish population [7, 8]. However metformin alone is often not enough to keep glycaemia under control and there is a substantial need for a second line anti-diabetic drug in HF participants. Unfortunately, the choices are very limited for the participants in this group. Sulphonylureas (SU) are commonly prescribed in T2D however they are associated with weight gain and hypoglycaemia, while there remain concerns that SUs may increase all-cause and cardiovascular-mortality,[9] although this link is not fully established. Glitazones are contra-indicated in New York Heart Association III or IV HF, while their role in milder degrees of HF remains to a certain extent controversial with some observational studies indicating increased hospitalisation or readmission due to HF.[10] Insulin use has also been associated with increased mortality in participants with CHF.[11] More recent agents such as the DPPIV inhibitors have also, disappointingly, failed to show cardiovascular benefit with some concerns raised following the publication of SAVOR-TIMI-53, that they increased HF hospitalisations, although these trials have only been of short duration[12] and may not apply to all DPPIV inhibitors (http://www.medscape.com/viewarticle/843830). Therefore, it can be concluded that therapeutic options in T2D and HF are very limited and there is a critical need for agents that will both improve overall glycaemic control and HF outcomes.

1.2 RATIONALE FOR TRIAL

In this trial it is proposed that there may be unique features of the SGLT2 inhibitors that exhibit renoprotective effects alongside cardioprotective effects in participants with mild-CHF with left ventricular systolic dysfunction and diabetes.

SGLT2 inhibitors have recently been licensed for use in participants with T2D. This oral anti-diabetic agent achieves its effect by blocking the low affinity, high capacity Type 2 Sodium-Glucose Linked co-Transporter, predominantly found in the proximal convoluted tubules of the kidneys, thus causing glycosuria, resulting in lowered blood glucose levels. SGLT2 inhibitors cause weight reduction following the caloric loss from glycosuria. They have also been shown to improve insulin resistance in ZDF rats[13] and in a small clinical trial among T2D participants.[14] Exercise intolerance is a cardinal symptom of participants with HF and improving insulin sensitivity has been shown to improve exercise capacity. Thus, SGLT2 inhibition has the potential to improve exercise capacity in SGLT2 inhibition and to have beneficial effects on adverse left ventricular (LV) remodelling that occurs in participants with DM and HF by reducing the load on the heart through its diuretic and blood pressure lowering actions. The recent landmark EMPA-REG outcome trial that reported a striking 35% relative risk reduction in HF hospitalisations with empagliflozin may provide supportive evidence for beneficial effects of SGLT2 inhibition in the setting of CHF.[15, 16] However, it should be noted that in the EMPA-REG trial, only 10% of trial participants had HF. The currently recruiting, European Foundation for the Study of Diabetes funded REFORM Trial is examining the potential LV remodelling benefits of SGLT2 inhibitors in participants with T2D and HF (clinical trials.gov identifier NCT02397421).

A significant problem among participants with T2D and concomitant HF is diuretic resistance.[17] It occurs frequently and can increase the length of stay in hospital and is associated with increased morbidity and mortality.[18] The pathophysiology of diuretic resistance is varied and remains the subject of much debate.[19] As a result, it is unclear how to treat diuretic resistance. At this time, sequential nephron blockade with thiazide-like diuretics used in combination with loop diuretics is often used to overcome diuretic resistance in acute decompensated CHF.[20] However this strategy does not always work and is associated with the hazards of hypokalaemia, hyponatraemia, hypotension and renal failure. A new strategy is needed. It is believed that SGLT2 inhibitors may be able to address this issue by its novel mechanism of action in the proximal part of

the renal tubules. It is hypothesized that its osmotic diuretic effects may augment the diuretic effects of furosemide in participants with T2DM and CHF.

There is data to support the potential for direct renoprotective actions arising from SGLT2 inhibition including actions to attenuate type 1 diabetes associated hyper filtration through an effect on tubulo-glomerular (TG) feedback which may have renal-protective effects by decreasing glomerular hydrostatic pressure.[23, 24] SGLT2 inhibition has also been shown to attenuate tubular hypertrophy and reduce the tubular toxicity of glucose.[22] They may also have indirect renoprotective effects through its blood pressure lowering effects and glycaemia lowering effects which could decrease the renal inflammatory and fibrotic response by blocking glucose entry into the cell.[22] Consequently, there are now several on-going SGLT2 inhibitor renal outcome trials in T2D, including the CANVAS-R trial (clinicaltrials.gov identifier NCT01989754) and the CREDENCE trial (clinical trials.gov identifier NCT02065791). However, neither trial specifically looks at T2DM participants with CHF.

We contend that these effects, albeit modest, of SGLT2 inhibitors may potentially augment the diuretic effect of loop diuretics. It is noteworthy that osmotic diuretics such as mannitol have been used alone or in combination with loop diuretics such as furosemide to promote diuresis in participants undergoing intra-cranial surgery[28] and in the postoperative period to prevent acute kidney injury.[29] In CHF, mannitol was reported to promote effective diuresis in a single centre trial in the US.[30] Importantly, in all these settings, mannitol, which is a potent osmotic diuretic when used in combination with furosemide, was shown to be safe and did not result in renal failure or electrolyte disturbances.

It is known that increased sodium delivery to the macula densa following SGLT2 inhibition may intensify TG feedback and lead to a decline in glomerular filtration rate at least in T2D individuals.[25, 26] A meta-analysis on the effect of dapagliflozin on renal function that included 12 placebo controlled randomized studies and involved more than 4000 participants with preserved renal function showed that dapagliflozin caused a fall in estimated glomerular filtration rate (eGFR) at week 1 that slowly returned to baseline.[31] This pattern of acute eGFR decline followed by stabilization suggests that the acute eGFR decline reflects a (reversible) haemodynamic change rather than worsening of structural renal function.

The renal effects of SGLT2 inhibitors in combination with furosemide in T2D with CHF are not known. The recent EMPA-REG trial demonstrated a beneficial effect of the SGLT2 inhibitor empagliflozin on cardiovascular outcomes, particularly heart failure hospitalisation in T2D.[15] It is thought that the most likely explanation for this positive result is the improvement in loading conditions caused by the osmotic diuresis.[33] Therefore, there is an urgent need for a trial to provide detailed acute and long-term information regarding the renal effects of the SGLT2 inhibition in combination with furosemide, in T2D participants with stable CHF.

The intent of this proposed trial is to obtain data that might be relevant to the design of future studies in which SGLT2 inhibitors may be considered as an adjunctive agent to loop diuretics in this vulnerable participant group. There is currently no data on combining SGLT2 inhibitors and diuretics, which is why this combination is not recommended at this point in time. However, it should be noted that in EMPA-REG 43% of participants were on loop diuretics.[15] Since HF and T2D are frequent co-morbidities, it is possible that physicians may find participants requiring both SGLT2 inhibitor therapy and furosemide concurrently. Only by trialling this, can these fundamental issues be addressed and, perhaps, inspire a change in practise.

We will recruit diabetic HF participants taking stable doses of furosemide, or, alternative loop diuretics, with eGFR greater than 45ml/min. Whilst SmPC states that empagliflozin should not be administered with an eGFR < 60 ml/min, EMPA-REG recruited participants with an inclusion criteria of eGFR ≥ 30 ml/min.[15] Within the total number of participants, n = 1819 (25%), with an EGFR < 60 mls/min, 1,212 were randomised to empagliflozin[15]. There was no reported increase in renal adverse events (acute kidney injury or hyperkalaemia) in those with eGFR < 60 mls/min regardless of whether the patients had impaired kidney function at baseline. Further analysis in the EMPA-REG renal outcome, demonstrated that in patients with T2D at high risk for cardiovascular events, those who received empagliflozin in addition to standard care had a significantly lower risk of microvascular outcome events than did those receiving placebo, a difference that was driven by a lower risk of progression of kidney disease (as defined by incident or worsening nephropathy).[32] Furthermore the Dapa-HF trial (clinical trials.gov identifier NCT03036124) will set an inclusion of eGFR > 30mls/min to further evaluate the effect of dapagliflozin on the incidence of worsening HF or cardiovascular death in patients with CHF.

As there will be administration of intravenous furosemide of half the participant's usual daily dose with the RECEDE-CHF protocol, an eGFR ≥ 45 ml/min will be taken as a cut off for inclusion.

This trial will, with careful monitoring, begin the process of uncovering the unrealised potential of this new class of drug, and for the reasons given above, it is poised to become the 2nd line anti-diabetic agent of choice in HF participants.

2 TRIAL OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary aim/objective will be to assess whether empagliflozin (SGLT2 Inhibitor) can augment the diuretic effect of loop diuretics in diabetic participants with mild CHF with left ventricular systolic dysfunction (LVSD), as measured by urinary volume, when compared to placebo.

2.1.2 Secondary Objectives

The secondary aims/objectives are to assess the effect of empagliflozin (SGLT2 inhibitor) on natriuresis when used with loop diuretics in diabetic patients with mild CHF with LVSD as measured by urinary sodium excretion, to measure the safety of add-on SGLT2 inhibitor therapy versus placebo on top of loop diuretics as measured by serum creatinine and eGFR, to assess effects of empagliflozin on protein/creatinine ratio, albumin/creatinine ratio and on the renal biomarker, cystatin C.

2.2 OUTCOMES

2.2.1 Primary Outcome

The primary outcome for this trial is:

- To assess the effect of empagliflozin versus placebo on urine output

2.2.2 Secondary Outcomes

The secondary outcomes for this trial are:

- To assess the effect of empagliflozin versus placebo on urinary sodium excretion
- To assess the change in glomerular filtration rate (safety endpoint)

- To assess the change in creatinine (safety endpoints)
- To assess the effect of empagliflozin on protein/creatinine ratio
- To assess the effect of empagliflozin on albumin/creatinine ratio
- To assess the effect of empagliflozin on the renal biomarker, cystatin C.

3 TRIAL DESIGN

3.1 TRIAL DESCRIPTION

The RECEDE-CHF Trial is a single centre randomised, double-blind, placebo-controlled, crossover, trial conducted in NHS Tayside to compare the SGLT2 inhibitor empagliflozin 25mg, to placebo. Participants will be enrolled in the trial for a period of between 14 to 16 weeks.

At the screening visit, following informed consent, an initial medical history and clinical examination will be performed and concomitant medication will be recorded. Participants will have bloods taken for safety analysis and vital signs will be checked to confirm eligibility prior to enrolment. An assessment of suitability of the trial for the potential participant will be undertaken by the principal investigator or medically qualified delegate.

Should the participant meet the inclusion criteria and have no exclusion criteria identified, they will return for the baseline/randomisation visit at the Clinical Research Centre (CRC), Ninewells Hospital, Dundee, within four weeks post screening visit. Where possible the screening visit and randomisation visits will be combined.

At the randomisation visit participants will undergo safety blood tests, vital signs and trial medication will be dispensed (either empagliflozin 25mg or placebo).

Participants will continue on trial medication, empagliflozin 25mg or placebo, once daily, for a period of 6 weeks. Participants will be educated on the symptoms of hypoglycaemia which includes a written action plan on how to manage it in the unlikely event that it occurs.

Participants will return to the CRC 3-days (±2 days) post-randomisation, for a trial day, lasting approximately 5 hours, where they will have safety and research bloods drawn, vital signs recorded and will undergo renal physiological tests (RPT). Participants will be required to provide several urine samples throughout the course of the visit.

Participants will then return again at week 6 for a trial day, lasting approximately 5 hours, where they will undergo RPT again, safety and research bloods will be drawn and vital signs recorded. Participants will be again required to provide several urine samples throughout the course of this visit. Participants will terminate trial drug, either empagliflozin 25mg or placebo, at this visit and will return to the CRC at the end of the two week wash out period (week 9)

At week 9, participants will have safety and research bloods drawn, vital signs recorded, new trial medication dispensed, educated on the symptoms of hypoglycaemia and given a written action plan on how to manage it in the unlikely event that it occurs.

Participants will subsequently return to the CRC after 3 days (±2 days), for a trial day, lasting approximately 5 hours, where they will have safety and research bloods drawn again, vital signs recorded and will undergo renal physiological tests (RPT). Participants will be required to provide several urine samples throughout the course of the visit.

Participants will then return again at week 14 for the final trial day, lasting approximately 5 hours, where they will undergo RPT again, safety and research bloods will be drawn and vital signs recorded. Participants will be required to provide several urine samples throughout the course of the visit. Participants will terminate trial drug, either empagliflozin 25mg or placebo.

Further details of trial visits are detailed in section 7.1.

Participants not on insulin will continue with all usual medications, these remain unchanged throughout unless clinically indicated. Participants who are already on insulin at time of recruitment will be advised of the likelihood of having to reduce their total daily dose of insulin by for example by a reduction of 10% on the day they are randomised with an increase in the frequency of their blood sugar monitoring. Further dose titration will be done by the trial team, Diabetic Consultant, or GP with or without instruction from either the trial team or Diabetic Consultant, based on the participant's symptoms, home and laboratory-based blood sugar levels. Down-titration of therapy will be done in a stepwise manner starting with insulin. Other anti-diabetic agents will only be down-titrated once insulin has been discontinued. Up-titration of therapy can be done at the treating physician's discretion. There will be no titration of the IMP.

Acute exacerbations of CHF are likely to occur in the course of this trial. These will be treated as per usual practice and the empagliflozin or placebo will not need to be stopped unless the participant or their clinician specifically requests stopping or there are sound clinical reasons to do so. Anti-hyperglycaemic medications may be adjusted by the participants GP, hospital care consultant or PI as necessary during the trial; changes will be recorded in the concomitant medications.

It is expected that the number of participants requiring therapy changes will be equal between the two groups. Participants experiencing two or more severe hypoglycaemic episodes, requiring medical assistance, despite down titration or discontinuation of other anti-hyperglycaemic medications will have trial medication discontinued.

3.2 TRIAL INVESTIGATIONS

3.2.1 Blood Tests

Screening blood samples will be taken for routine haematology and biochemistry tests including full blood count, renal function, (U&Es), liver function (LFTs), blood glucose, haemoglobin A1c, lipids, pro-NT BNP and cystatin C levels.

Routine safety bloods will be taken at visits throughout the trial: at each visit, in pre-screening, baseline/randomisation, visits 3 (day 2), visits 5 (week 6) visit 6 (week9) visit 7 (week 9 + 3) and the final visit week 15.

Research bloods will be taken at randomisation visit, day 3, week 6, week 9 (post-wash out), week 9 day 3, and week 15. BNP, inflammatory markers and other markers of interest such as oxidative stress will be measured. Additional blood markers may be tested on surplus samples at a later date. The total amount of research blood taken at each visit will be no more than 20ml.

Consent will also be sought for future ethically approved genetic analysis using research blood samples. This can be declined without affecting participation in the trial. If agreement is given for this, 10ml of extra blood will be taken at the randomisation visit and anonymously stored in the Division of Molecular and Clinical Medicine, University of Dundee: any subsequent analysis of these samples will be subject to approval of a Research Ethics Committee (REC) prior to analysis.

3.2.2 Urine Tests

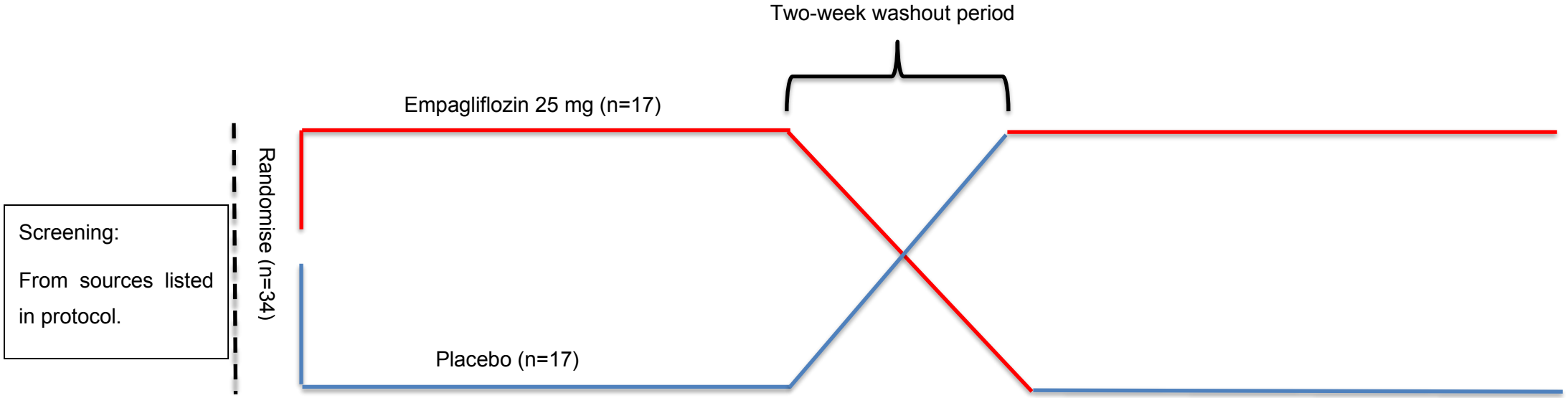
Participants will provide a spot urine sample for quantification of albumin/creatinine ratio and protein/creatinine ratio at 4 of the trial days. As well as four 24 hour urinary collections on the days prior to the renal physiological tests days.

3.2.3 Renal Physiological Tests

Participants will attend the Clinical Research Centre (CRC) on 4 separate trial days (2 while in each arm of the trial). On each trial day, participants will present themselves to the CRC, following an overnight fast. Two days before presenting to the CRC, participants will be required to follow a 2gm sodium and 2L fluid/day controlled diet. A 24-hour urine collection will be made in the 24 hours prior to the day of the renal physiological test. Participants will be asked to take their morning usual medications except their IMP (empagliflozin or placebo) and furosemide (or equivalent loop diuretic).

An intravenous cannula will be placed in each arm for subsequent infusion and blood sampling. Bloods will be drawn for measurement of plasma NT-proBNP (a biomarker of wall stress and will be measured as a discovery variable in this proof of concept trial) using standard protocols. Firstly, a 15 ml/kg oral water load will be administered over approximately a 15-minute period. Thereafter, at approximately 30 minute intervals, participants will be requested to void urine until the end of the trial day. The volume of urine passed will be measured and an aliquot stored for later analysis. On each occasion, the volume of urine passed will be measured, and an equal volume of water given to drink. In this way, a steady state diuresis will be established over approximately 3 hours. The last urine collection during this stabilization period will be taken as baseline. Approximately 3 hours after initiation of the test, each participant will receive an oral tablet of either empagliflozin 25mg or placebo. After the seventh urine sample, participants will be given a bolus of IV furosemide at half their total daily dose. Heart rate will be displayed continuously on an ECG oscilloscope and the blood pressure measured approximately every 60 minutes. Venous blood will be obtained at the midpoint of each clearance period for measurement of serum sodium, osmolality and creatinine. At the end of the RPT, light refreshments in the form of tea, coffee or juice with biscuits will be provided. A lunch will then be provided at the CRC.

3.3 TRIAL FLOWCHART



Up to 4 weeks before randomisation.	Day 0 Randomisation	Day 3 RPT	Week 3 Televisit	Week 6 RPT	Weeks 7-9 Washout period	Week 9 Drug dispensing	Week 9 + Day 3 RPT	Week 12 Televisit	Week 15 RPT

Please refer to Section 7 and Appendix 1 for more detailed information regarding study specific tests being performed at each visit.

4 TRIAL POPULATION

4.1 NUMBER OF PARTICIPANTS

34 participants with underlying diabetes and well-controlled chronic heart failure (CHF) will be recruited from a range of sources as listed below in 5.1.

The PI will be responsible for recruitment but may delegate to other named individuals within the trial team. Any such delegation will be recorded on the trial delegation log and authorised by the CI.

It is anticipated it will take up to 18 months to recruit the 34 participants for randomisation with approximately 80-100 being consented into the screening trial. We anticipate a screen failure rate of 20% and a dropout rate of 35% after recruitment due to the high intensity and frequent renal physiological tests.

4.2 INCLUSION CRITERIA

Participants will be eligible if they:

- Aged 18 to 80 years with previously diagnosed Type 2 Diabetes Mellitus.
- Are diagnosed with NYHA Functional class II-III HF with prior echocardiographic evidence of LVSD.
- On stable doses of furosemide, or alternative loop diuretic for at least one month.
- Type 2 Diabetes
- eGFR ≥ 45 ml/min.
- Have stable HF symptoms for at least three months prior to consent
- On stable HF therapy for at least three months prior to consent
- Have not been hospitalised for HF for at least three months prior to consent.
- Women of childbearing potential* (WoCBP) must agree to take precautions to avoid pregnancy throughout the trial and for 4 weeks after intake of the last dose.

4.3 EXCLUSION CRITERIA

Participants will be excluded if they:

- A diagnosis of chronic liver disease and/or liver enzymes that are twice the upper limit of normal
- Systolic BP of <95mmHg at screening visit.
- HbA1c < 6.0%
- Participants on thiazide diuretics.
- Participants receiving renal dialysis
- Participants who have previously had an episode of diabetic ketoacidosis.
- Participants with type 1 diabetes mellitus
- Malignancy (receiving active treatment) or other life threatening disease.
- Pregnant or lactating women
- Participants with difficulty in micturition e.g. severe prostate enlargement
- Allergy to any SGLT2 inhibitor or lactose or galactose intolerance
- Past or current treatment with any SGLT2 inhibitor
- Participants who have participated in any other clinical interventional trial of an investigational medicinal product within 30 days.
- Participants who are unable to give informed consent
- Any other reason considered by the physician to be inappropriate for inclusion.

*Women of child bearing potential (WoCBP) are defined as premenopausal women who have not been surgically sterilised or had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy. Women over 45 years old, who have not had a menstrual period for at least 12 months, without an alternative medical cause, will be considered post-menopausal.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be recruited from the sources identified as:

1. From the HF (BIOSTAT) database in Tayside of research participants who have taken part in previous HF studies in the Department of Clinical Pharmacology, University of Dundee.
2. From the Diabetes and Cardiology clinics at any of the four NHS Tayside locations (Ninewells Hospital, Arbroath Royal Infirmary, Stracathro Hospital and Perth Royal Infirmary).
3. From SHARE, the Scottish Health Research Register, where participants have pre-consented to be invited for research.
4. From the Scottish Diabetes Research Network (SDRN), where patients have previously been involved in diabetes trials and have consented to being approached for future research, including those registered on the GoDARTS Database.

The PI will be responsible for recruitment but may delegate to other named individuals within the trial team. The PI or delegate may remotely screen electronic records to identify potentially suitable people and appropriate approvals will be in place to allow them to do so.

5.2 CONSENTING PARTICIPANTS

The PI, research nurse or delegate will either approach directly suitable participants at the clinical areas specified above or they will be approached indirectly by letter. Medical notes, which can be accessed via online systems such as Clinical Portal, will be reviewed to initially assess a participant's suitability. A review of the medical notes will be made to assess inclusion criteria (as listed in 4.2), and to identify if exclusion criteria (listed in 4.3) are met, prior to being approached. The letter will be sent either from their clinical consultant responsible for their care or from the CI, either directly or on his behalf by the UoD Health Informatics Centre (HIC), if required. Prior consent for contact is in place for participants registered to the research databases described above. Those registered with SHARE have also provided consent for access to and use of their electronic health records in order to identify them as potentially eligible participants for the trial.

When first contact is via letter (or telephone/e-mail if it is via SHARE, as per participant choice), a brief Participant Information Sheet (bPIS) will be sent which gives a general overview of the trial. Participants will be asked to contact the research team if they are

interested in the trial. All participants will be given at least 24 hours to consider their response and will be asked to return an expression of interest in a stamped, addressed envelope.

Should participants express an interest in taking part in the trial from the bPIS they will be provided with a full participant information sheet (PIS) by post. They will be given at least 24 hours to consider participation before they are scheduled to attend the research clinic at the CRC, Ninewells Hospital. When first contact is directly via a Clinic, potential participants will be given full PIS. All participants will be given at least 24 hours to consider participation before a screening visit is arranged by the research fellow or delegate.

Participants will have the opportunity to ask questions about the trial when the screening visit is being arranged and at the screening visit, where the informed consent discussion will take place. If they decide to participate, written informed consent will be taken and eligibility assessed by confirming all inclusion/exclusion criteria – medical notes will also be reviewed again at this stage. The CI, PI, research nurse or appropriately trained and qualified delegate will carry out informed consent.

Where a participant requests to speak with a physician from the trial team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

Participants will be asked for their consent for a member of the Research team (CI, PI or research nurse) to inform the GP of the individual's intent to participate in this study. Those participants who do not agree to their GP being informed of participation in this study will be excluded from the study.

All individuals taking informed consent will have received training in Good Clinical Practice (GCP) and will adhere to the TASC SOP07 on informed consent. It will be explained to participants that they are under no obligation to enrol in the trial and that they can withdraw at any time during the trial, without having to give a reason. A copy of the signed informed consent form (ICF) along with a copy of the PIS will be given to the trial participant. The original signed consent form will be retained at the trial site (filed in the TMF) and one copy filed in the medical notes.

5.3 SCREENING FOR ELIGIBILITY

Participants must have documented Type 2 Diabetes Mellitus and CHF with LVSD. Post consent, screening bloods will be performed to ensure renal function and HbA1c meet the inclusion criteria. Blood pressure and heart rate will also be measured. Women of child bearing potential will have a pregnancy test. Participants will be consented prior to screening and a screening log will be maintained.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

The reason(s) for ineligibility will be explained to participants and any questions they have will be answered. They will be thanked for their participation in screening and any relevant information from this will be added to their hospital notes and be communicated to their GP and consultant, where the participant consents for this to happen.

5.5 RANDOMISATION

5.5.1 Randomisation

After successful screening for eligibility and safety, participants will be randomised to either empagliflozin 25mg/ placebo or placebo/empagliflozin 25 mg in a double blind fashion in this crossover study.

The double blind medication (empagliflozin or placebo) will be prepared, packaged and labelled by Tayside Pharmaceuticals. Randomisation will be carried out by Tayside Pharmaceuticals, using block randomisation using a validated randomisation programme, and will securely backup both the randomisation seed and the randomisation allocation.

The Clinical Trials Pharmacy, Ninewells Hospital will be provided with a copy of the randomisation allocation for the purposes of 24h emergency unblinding.

5.5.2 Treatment Allocation

Participants will be given blinded medication. At the randomisation visit they will be dosed with either empagliflozin 25mg (6 weeks) or matched placebo (6 weeks) to continue once daily, with a 2-week washout period between each arm. Participants and their bloods (including U&Es and LFTs, FBC) will be monitored as per trial schedule and medication stopped if concerns arise. If trial drug needs to be stopped

due to intolerance or adverse events, they will remain in the trial in order to do an "intention to treat" analysis. They will be invited to attend all future trial visits.

5.5.3 Emergency Unblinding Procedures

A clinician familiar with the research (and named on the delegation log) will be available each workday for contact by all participants. This will include the CI, the PI/ a research fellow based within the Division of Cardiovascular and Diabetes Medicine Department at Ninewells Hospital.

Any other clinician who sees participants during trial participation will be free to stop the trial drug if they feel it is clinically indicated and be asked to inform the trial team. The Clinical Trials Pharmacy, Ninewells Hospital will be provided with a copy of the randomisation allocation for the purposes of 24h emergency unblinding. During office hours the Clinical Trial Pharmacy, Ninewells Hospital, should be contacted if unblinding is required, out of hours the On-call Pharmacist should be contacted via Ninewells Hospital switchboard.

5.5.4 Withdrawal procedures

Participants are free to withdraw from the trial at any time. Although a participant is not obliged to give reason(s) for withdrawing prematurely, if the participant appears lost to follow up, the CI will make a **reasonable** effort to ascertain the reason(s), while fully respecting the individual's rights, and will demonstrate that everything possible was done in an attempt to find any participant lost to follow-up. Those lost to follow-up or withdrawn will be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

Participants who withdraw will be replaced if possible within the trial time frame. Those that withdraw from trial drug will be encouraged to attend future trial visits and where possible the final visit for the outcome measures. Participants who withdraw will be invited to a final 'early discontinuation' visit. At this visit, the tests that would be taken at week 15 the final study visit, including vital signs and blood samples for NT-proBNP, serum sodium, osmolality and creatinine, for safety, research and genetic bloods (without undergoing the detailed renal physiological testing), to allow the investigators to obtain further information on the safety of the drug.

If withdrawal is due to an adverse event (AE), contact will be maintained by the PI or delegate with the individual to ensure resolution of the AE; this will also be logged in the AE log and participant's hospital case notes.

Reasons for treatment discontinuation due to safety and/or tolerability are listed in section 6.8. There is an increased risk of hypoglycaemia, as discussed in section 10.2

Participants' anti-hyperglycaemic medications may be adjusted as deemed necessary by a trial doctor, local NHS clinic or GP in order to achieve an appropriate individualised glycaemic control according to local guidelines without them having to stop the trial medication. Medications will be reconciled at all 9 patient visits (see Appendix 1) so that documentation can be made of any changes to participants' other regular medication. Where medication has been adjusted, the Emergency Care Summary, an online patient record used to document repeat and acute prescriptions will be used to clarify the start and stopping date for any medication changes. Changes made by Hospital based doctors will be seen on Medical documentation and clinic letters. If clarification is required for changes made in the community, then the GP Practice may be contacted directly to clarify the date and indication for change.

6 INVESTIGATIONAL MEDICINAL PRODUCT

6.1 TRIAL DRUG

6.1.1 Trial Drug Identification

Jardiance tablet (25mg) over-encapsulated in hard gelatine capsule shell.

6.1.2 Trial Drug Manufacturer

Tayside Pharmaceuticals, Ninewells Hospital, Dundee.

6.1.3 Marketing Authorisation Holder

Not applicable. IMP dossier to be formulated by Tayside Pharmaceuticals

6.1.4 Labelling and Packaging

Tayside Pharmaceuticals, Ninewells Hospital, Dundee.

6.1.5 Storage

IMP will be stored in the Clinical Trial Pharmacy (Ninewells Hospital, Dundee). IMP accountability logs will be held in the Pharmacy Site File (PSF).

6.1.6 IMP Safety Information

The Summary of Product Characteristics (SmPC) will be held in the PSF and TMF. Section 4.8 will be used to assess the causality of any adverse event in relation to the IMP. The CI will check at least annually for any changes to the SmPC. Where changes to Section 4.8 impact on the assessment of causality of adverse events, the new version of the SmPC will be submitted as an amendment prior to being used as reference safety information (RSI) and the updated SmPC will be provided to Pharmacy.

Common side effects of empagliflozin include, increased urination and vaginal yeast infection. Women who take empagliflozin may get vaginal yeast infections hence participations will be encouraged to approach either the PI or the GP if they experience vaginal odour, white or yellowish vaginal discharge and/or vaginal itching. Increased urination may be reported by the participant in the absence of any infection. Less common side effects include, dehydration and subsequent acute kidney injury, ketoacidosis (which has been reported in the absence of hyperglycaemia), urinary tract infections, hepatic injury and for men taking empagliflozin, yeast infection of the penis.

6.1.7 Accountability procedures

These will be overseen by the Clinical Trials Pharmacist in the Clinical Trials Pharmacy Department (Ninewells Hospital) and will be documented in an Accountability Log held in the PSF. Accountability will be in compliance with TASC SOP 37.

6.2 TRIAL COMPARATOR

6.2.1 Comparator Identification

Hard gelatine capsule shell containing Microcrystalline Cellulose Ph. Eur.

6.2.2 Comparator Manufacturer

Tayside Pharmaceuticals, Ninewells Hospital, Dundee.

6.2.3 Labelling and Packaging

Tayside Pharmaceuticals, Ninewells Hospital, Dundee.

6.2.4 Storage

Drugs will be stored in the Clinical Trial Pharmacy (Ninewells Hospital).

6.3 DOSING REGIME

Participants will be given blinded medication. At the randomisation visit, they will be dosed with either oral empagliflozin 25mg OD or matched placebo to continue for 6 weeks, if tolerated. This will be followed by a two-week washout period. The participant will then cross over to be given either placebo or empagliflozin 25mg OD for a further 6 weeks.

No additional lifestyle restrictions will be imposed on the participant and we will ask them to carry on as normal except in the 48 hours preceding the renal physiological tests where we would request a 2gm sodium and 2L fluid/day controlled diet**DOSE CHANGES**

No dose change is planned in this trial. If the participant is taken off the trial, their GP and/or consultant will be informed of the reason for that.

6.5 PARTICIPANT COMPLIANCE

Compliance will be checked and documented using tablet counts at both trial visits during each arm. A telephone visit is scheduled for week 3 and week 12 where compliance will be checked verbally and participants will be advised by the research nurse or PI on the importance of correct compliance.

6.6 OVERDOSE

This is unlikely given the simple once daily dosing but there is no specific antidote.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the participant's clinical status. The removal of empagliflozin by haemodialysis has not been studied.

Overdose with empagliflozin is rare, however it has been noted that there is an increased risk of hypoglycaemia when given with insulin and/or sulphonylureas. The majority of the hypoglycaemic events are mild (defined as not requiring any assistance). In the case of any overdose, the patient will be advised to stop the medication and the event will be reported. If symptomatic, the patient (or their carer) will be advised to take an oral glucose load (sugary drink, fruit etc.) and if necessary to seek medical attention at their GP or hospital.

6.7 OTHER MEDICATIONS

6.7.1 Permitted Medications

Other medications, apart from those listed in 6.7.2, will be allowed. All concurrent medication(s) will be recorded.

6.7.2 Prohibited Medications

Repaglinide, and other anti-diabetic drugs in this class are contra-indicated due to the increased risk of hypoglycaemia. Thiazide diuretics due to increased risk of hyper diuresis. These medications are prohibited in this trial. The GP information letter and PIS will contain information on all the above points.

6.7.3 Concomitant Medications

Details of all concomitant medications will be discussed and recorded in the CRF at all study visits, including telephone visits.

6.8 DISCONTINUATION

The trial medication will be discontinued due to safety and/or tolerability in the following circumstances:

- Participant becomes pregnant
- LFTs rise to greater than twice the normal range
- Participant develops symptoms of NYHA class IV heart failure
- Participant has vomiting and diarrhoea for 48 hours and volume depletion is suspected
- Participant develops symptomatic postural hypotension
- Participant develops signs of vulvovaginitis, balanitis and related genital infections or urinary tract infections which do not respond to treatment.
- Participant has suspected or diagnosed Diabetic Ketoacidosis
- Participant develops a sustained eGFR < 45 mls/min despite alteration of dose of furosemide or alternative loop diuretic

7 TRIAL ASSESSMENTS

7.1 TRIAL ASSESSMENTS

As outlined in section 5.2, participants will be provided with a full PIS and are given at least 24 hours to consider their response before a screening visit will be arranged for consent to be taken and to check their eligibility by all the criteria. On discussion with the participant, if they are willing to wait for the results of their safety blood tests, visit 1 (screening) and visit 2 (baseline/randomisation) will be offered to be combined.

For details of assessments carried out at each visit see Appendix 1

7.2 SAFETY ASSESSMENTS

Safety assessments will be carried out at visits 1 (screening), 2 (baseline/randomisation) or where visits 1 and 2 (screening and baseline/randomisation) are combined, visit 3 (Day 3), visit 5 (week 10), visit 6 (week 9), visit 7 (week 9 ±3) and visit 9 (week 15). Participants will be asked to return for visit 10 (final visit/week 19 ± 7 days) to ensure diuretic medication is at an adequate dose following discontinuation of study medication. These safety assessments include:

- Safety bloods: including U&Es, LFTs, Glucose, Magnesium, Calcium, Cholesterol, Urate and FBC
- Vital signs including BP, participants will be asked about any symptoms of postural hypotension and hypoglycaemia
- Assessment of any adverse events (specifically genital infection as this is the most common side effect of empagliflozin and may present as an adverse reaction).

8 DATA COLLECTION& MANAGEMENT

8.1 DATA COLLECTION

The data will be collected by the PI or delegate on a paper case report form (CRF) with subsequent transcription to an electronic CRF. Electronic storage will be in an encrypted form on a password protected device.

The medical notes will act as source data for past medical history and blood results. Any data relating to general medical history will be documented in the notes.

8.2 DATA MANAGEMENT SYSTEM

Excel will be used as the data management system (DMS) with adherence to TASC SOP 48 Data Management in CTIMPs using Excel, by the trial team doing the data entry and analysis.

The DMS will be based on the protocol and CRF for the trial and individual requirements of the investigators. Development and validation of the trial database and QC will be done according to TASC SOP 48.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

9.1.1 POWER CALCULATIONS

Power calculations are based on our previous data in participants with CHF[36-40] as well as more contemporary data.[41] The sample size is based on the mean furosemide-induced urinary volume (SD=250). A 20% increase is expected in this parameter following SGLT2 inhibition. This increase in urinary volume is based on published percentage increases in urinary volume in T2D patients that range from 11%-33% depending on the dose of the SGLT2 inhibitor as shown by List and colleagues[42] in the available data with dapagliflozin (dapagliflozin 2.5 mg: 11% increase in 24-hr urine volume; dapagliflozin 5 mg: 22% 11% increase in 24-hr urine volume; dapagliflozin 10 mg: 24% 11% increase in 24-hr urine volume; dapagliflozin 20 mg: 27% 11% increase in 24-hr urine volume and dapagliflozin 50 mg: 33% 11% increase in 24-hr urine volume). There is no data of SGLT inhibition together with loop diuretics apart from the previously discussed case report of a diuretic resistant HF patient in whom the fluid overload was successfully treated with the SGLT2 inhibitor, ipragliflozin. The authors reported a striking 50% increase in urinary volume (following treatment with 50 mg daily of oral ipragliflozin for 5 days).[34] Based on the above, it was determined that a 20% increase in furosemide induced increase in urinary volume will be reasonable.

With an alpha 0.05 and power of 90%, 22 participants per arm are required, assuming 35% drop out. Since this trial is using an AB/BA crossover design, a total of 34 participants will be required, as each participant will be exposed to both arms of the

trial. The rationale for the high dropout rate, is due to the high intensity renal physiological tests that will occur on 4 occasions for the participants, from 0730 to 1230 we feel that anything less than a 35% drop out rate would be conservative.

9.2 PROPOSED ANALYSES

9.2.1 STATISTICAL ANALYSIS

Participants will be allocated to treatment groups at random. Descriptive statistics will be calculated for all data and reported as mean (SD) for continuous data and N (%) for categorical data. For statistical evaluation of repeated measurements, analysis of variance will be used. $P<0.05$ will be taken as the level of statistical significance.

A detailed statistical analysis plan will be prepared during the trial by the trial statistician.

9.3 MISSING DATA

The primary analysis will be based on the intention-to-treat principle. The extent of missing data will be examined and the reason for the dropout ascertained. Multiple imputation may be used to impute missing values if necessary and where assumptions for missing at random (MAR) data are met. Complete case analysis where missing participants are excluded will be carried out as a secondary analysis. Pre-specified sub-group analyses will be completed by fitting the appropriate interaction term in the regression model and- if significant outcomes will be presented separately by level of sub-group.

With regards to participant medication, this will be recorded at baseline and at each trial visit with a secondary analysis adjusting for changes in trial medications planned.

10 ADVERSE EVENTS

Adverse event reporting will be carried out in accordance with TASC SOP 11: Identifying, Recording and Reporting Adverse Events for Clinical Trials of Investigational Medicinal Products. The CI (or delegate) is responsible for detection and documentation (and reporting, where required) of adverse events.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness

and may be reclassified as a serious event or reaction based on prevailing circumstances.

An **adverse reaction** (AR) is where it is suspected that an AE has been caused by a reaction to a trial drug.

A serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR) is any AE, AR or UAR that at any dose:

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- Or is otherwise considered serious

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. However, any adverse events occurring during such hospitalisation will be recorded.

10.2 DETECTING AES AND SAES

The CI is responsible for the detection and documentation of events meeting the criteria and definitions below.

Full details of contraindications and side effects that have been reported following administration of the trial drug can be found in the SmPC. Adverse reactions in association with empagliflozin are rare in the overall treated population and mostly of a minor nature. The incidence may be higher in the presence of renal and/or hepatic disorder.

Common non-serious side effects are: Runny or stuffy nose; sore throat.

Severe side effects that may occur and which immediate attention should be sought are: Severe allergic reactions (rash; hives; itching; difficulty breathing or swallowing; tightness in the chest; swelling of the mouth, face, lips, throat, or tongue; unusual hoarseness); fainting; fast or irregular heartbeat; increased urination; muscle weakness; penis discharge, redness, rash, itching, pain, or swelling; severe or

persistent headache, dizziness, or light-headedness; sluggishness; symptoms of low blood sugar (e.g. confusion, increased sweating, weakness, tremors, dizziness, fainting, drowsiness, headache, irritability, chills, fast heartbeat, vision changes, increased hunger); symptoms of kidney problems or urinary tract infection (e.g. blood in the urine, change in the amount of urine produced, difficult or painful urination, unusual or persistent pain in the mid to lower back, unexplained swelling); unusual tiredness or weakness; vaginal discharge, itching, or odour, very dry mouth or eyes.

Participants should be instructed to contact a member of the trial team at any time after consenting to join the trial if any of the above symptoms develop. All reported adverse events (AEs) that occur after joining the trial will be recorded in detail in the CRF AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgement. Participants with AEs present at the last visit must be followed up until resolution of the event.

10.3 RECORDING AND REPORTING AES AND SAES

All AEs and SAEs will be recorded from the time a participant consents to join the trial until the last trial visit. Participants with unresolved AEs at their last trial visit will be followed up until resolution or 30 days after their last visit, whichever is sooner. SAEs and SUSARS will be followed until resolution.

The CI or delegate will ask about the occurrence of AEs and hospitalisations at every visit during the trial. AEs will be recorded on the AE Log in the CRF. SAEs will be submitted on an SAE form to the TASC Pharmacovigilance Section (pharmacovigilance.tayside@nhs.net) within 24 hours of becoming aware of the SAE. SAEs will be initially assessed for causality and expectedness by the Investigator. The Sponsor will make the definitive assessment on expectedness. The evaluation of expectedness will be made based on the knowledge of the reaction and the relevant product information (SmPC). Refer to TASC SOP 11 “Identifying, Recording and Reporting Adverse Events for CTIMPs”.

10.4 EVALUATION OF AES AND SAES.

Seriousness, causality, severity and expectedness will be evaluated as though the participant is taking an active drug.

10.4.1 Assessment of Seriousness

The CI or delegate will make an assessment of seriousness as defined in section 10.1.

10.4.2 Assessment of Causality

The CI or delegate will make an assessment of whether the AE is likely to be related to treatment according to the following definitions.

Unrelated: where the AE is not considered to be related to the trial drug.

Possibly: although a relationship to the trial drug cannot be completely ruled out, the nature of the event, underlying disease, concomitant medication or temporal relationship make other explanations more likely.

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the trial drug.

Definitely: the known effects of the trial drug or its therapeutic class, or based on challenge testing, suggest that the trial drug is the most likely cause.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the trial drug will be considered as ARs/SARs. All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the trial drug and another drug will also be considered to be ARs/SARs.

Alternative causes such as natural history of underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment will be considered. The blind will not be broken for the purpose of making this assessment.

10.4.3 Assessment of Severity

The CI or delegate will make an assessment of severity for each AE according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe by not serious, while a minor stroke is serious but may not be severe.

10.4.4 Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC Section 4.8.

ARs/SARs may be classed as either:

Expected: The AR is consistent with the toxicity of the trial drug listed in the SmPC.

Unexpected: The AR is not consistent with the toxicity in the SmPC.

10.5 REPORTING OF SAES/SURS/SUSARS

SAEs must be reported to the TASC Pharmacovigilance Section pharmacovigilance.tayside@nhs.net within 24 hours of the CI or delegate becoming aware of the event. The TASC SAE form must be completed as thoroughly as possible with all available details of the event and signed by the Investigator. If any of the information is not available at the time of reporting, the Investigator will ensure that any missing information is provided on a follow-up SAE form as soon as this becomes available. It will be indicated on the form that this information is follow-up information of a previously reported event.

All SAEs must be followed up to resolution and any additional information reported to the TASC Pharmacovigilance Section pharmacovigilance.tayside@nhs.net using the TASC SAE form.

10.6 REGULATORY REPORTING REQUIREMENTS

The Sponsor is responsible for reporting SUSARs to the competent authority, the MHRA, the Research Ethics Committee (REC) and any other competent authorities. Fatal or life threatening SUSARs will be reported within 7 days and non-fatal and non-life threatening SUSARs within 15 days.

10.7 ANNUAL REPORTING REQUIREMENTS

The following reports will be submitted each year as a condition of the authorisation to undertake a clinical trial or as a condition of a favourable opinion from REC.

The Development Safety Update Report (DSUR) will be prepared by the Sponsor - TASC Pharmacovigilance Section - and CI and submitted to the MHRA on the anniversary date of Clinical Trial Authorisation (CTA).

An NRES CTIMP Safety Report Form will be sent to REC along with the DSUR. Reports of SUSARs in the UK, urgent safety measures and any other safety reports submitted, for example reports of a data monitoring committee, will also be accompanied by a Safety Report Form.

A NRES Annual Progress Report for CTIMPs will be prepared and submitted by the CI to REC and copied to sponsor on the anniversary date of the REC favourable opinion.

10.8 URGENT SAFETY MEASURES

The CI or other clinician may take appropriate immediate urgent safety measures in order to protect the participants of a CTIMP against any immediate hazard to their health or safety. The MHRA, REC and Sponsor will be notified in writing within three days.

11 PREGNANCY

Pregnancy is not considered an AE or SAE, unless there is a congenital abnormality or birth defect. If a pregnancy occurs, the participant will be advised to stop trial medication immediately. The CI or delegate will collect pregnancy information for female trial participants who become pregnant, or female partners of male trial participants who become pregnant while participating in a trial.

For female partners of male trial participants who become pregnant while participating in a trial, additional consent should be obtained to follow up the pregnancy.

The CI or delegate should complete the TASC Pregnancy Notification Form and submit to the TASC Pharmacovigilance section pharmacovigilance.tayside@nhs.net within 14 days of being made aware of the pregnancy.

Any pregnancy should be followed to outcome. Pregnancy follow up information must be recorded on the TASC Pregnancy Follow up form and submitted to the TASC Pharmacovigilance section.

11.1 CONTRACEPTIVE ADVICE TO PARTICIPANTS

Women of child bearing potential must be willing to have pregnancy testing prior to trial entry, prior to administration of trial medication and during trial treatment. In addition, women of child bearing potential, who are sexually active, must be willing to use a form of a medically approved birth control method 7.1 e.g.:

- Combined Oral Contraceptive Pill
- Placement of an intrauterine device – 'coil'
- Barrier methods of contraception: male condom only
- Established use of oral, injected, transdermal or implanted hormonal methods of contraception
- Male partner sterilisation (followed by the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

Men who are sexually active with female partners of child bearing potential will also be advised to use a form of medically approved birth control method as listed above.

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be co-ordinated by a Trial Management Group, consisting of the grant-holders including the CI, the PI and the trial manager.

12.2 TRIAL MANAGEMENT

The PI will oversee the trial on a day-to-day basis and will be accountable to the CI. The PI will be responsible for checking the CRFs for completeness, plausibility and consistency. However, this will remain the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the trial team.

A trial-specific Delegation of Responsibilities & Signature Log will be prepared and maintained throughout the trial, detailing the responsibilities of each member of staff working on the trial.

12.3 TRIAL STEERING COMMITTEE

The Trial Management Group (TMG) will also act as the Trial Steering Committee (TSC).

12.4 DATA MONITORING COMMITTEE

This is not considered necessary as this is a relatively small trial. Close supervision of the PI/Clinical Research Fellow will be conducted by an experienced Chief Investigator supported by a senior trial manager from the TCTU.

12.5 INSPECTION OF RECORDS

The CI, PI and all institutions involved in the trial will permit trial related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all trial records and source documentation.

12.6 RISK ASSESSMENT

A trial risk assessment was carried out by the TASC Research Governance Manager prior to Sponsorship approval being granted.

12.7 TRIAL MONITORING

Trial monitoring will be in accordance with TASC SOP 03.
The purpose of trial monitoring is to verify that:

- The rights and well-being of human subjects are protected
- The reported trial data are accurate, complete and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The Sponsor will determine the appropriate extent and nature of monitoring for the trial and will appoint appropriately qualified and trained monitors.
The monitor will communicate any monitoring findings to both the CI and PI and the Sponsor.

12.7.1 Potential Risks

Potential adverse reaction to empagliflozin are outlined in the SmPC and discussed in section 10.2.

The participants will undergo venepuncture and cannulation which may cause some mild transient pain and bruising at the visits outlined in Appendix 1. Care will be taken by the doctor or nurse to minimise any distress to the participant. Needle stick injury during venepuncture remains a risk to the medical or nursing staff involved, and universal precautions will be taken. During the renal physiology tests, staff at the CRC will be handling urine collections, again universal precautions will be taken.

12.7.2 Minimising Risk

Careful monitoring of participant's blood results throughout the trial and dedicated care and adverse event monitoring will be undertaken as required. Participants who are on contraindicated medications will be excluded and those at higher risk of adverse events will also be prohibited from participating, as specified in the exclusion criteria.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT OF THE TRIAL

The trial will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from an appropriate REC. Authorisation from an appropriate competent authority(s) and appropriate NHS R&D permissions(s) will be obtained prior to commencement of the trial.

13.2 REGULATORY COMPLIANCE OF THE TRIAL

Regulatory approval will be obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, and any relevant amendments.

13.3 CI RESPOBSIBILITIES

The CI will be responsible for the overall conduct of the trial at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the CI.

Responsibilities may be delegated to an appropriate member of trial staff at each site. Delegated tasks must be documented on the Delegation Log and signed by all those named on the list and by the CI. The CI will supervise the clinical research fellow who will act as PI on the trial.

13.3.1 Informed Consent

The CI will be responsible for ensuring informed consents is obtained before any protocol specific procedures are carried out as the decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants will receive adequate oral and written information-appropriate Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be provided. The oral explanation to the participant will be performed by the PI (research fellow) or delegate and will cover all the elements specified in the PIS and ICF.

The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant will be given sufficient time to consider the information provided. It will be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and must agree to their medical records being inspected by regulatory authorities, REC and monitors but it will be explained that their name will not be disclosed outside the trial site.

The ICF will request permission that data collected from the participant by the Researcher and/or research team in this study will be used to support other research in the future, and may be shared anonymously with other researchers collaborating with the research team. The data will be stored electronically, anonymously and securely.

The ICF will request permission that any tissue (referring to urine and serum samples) collected by the Researcher and/or research team in this study will be stored and that any excess may be shared anonymously with other researchers collaborating with the research team to support future research projects. Any residual urine or serum samples would be stored anonymously in the secure University of Dundee laboratory in the Division of Cardiovascular and Diabetes Medicine for up to 10 years.

In the sharing of tissue (in this study which would be urine and blood samples) any future projects would require collaboration with the researchers and would require scrutiny from further Research Ethics Committee review.

The CI or delegate and the participant will sign and date the ICF to confirm that consent has been obtained. The participant will receive a copy of this document and a copy will be filed in their medical case notes and TMF as appropriate.

13.3.2 Trial Staff

The CI, PI and other appropriate trial staff will be familiar with the IMP, protocol and the trial requirements. The CI will ensure that all staff assisting with the trial are adequately informed and trained about the IMP, protocol and their trial related duties as appropriate. The CI will provide supervision of the PI, who is a research fellow on this trial.

13.3.3 Data Recording

The CI is responsible for the quality of the data recorded in the CRF.

13.3.4 GCP Training

All trial staff will hold evidence of appropriate valid GCP training or undergo GCP training and maintain this throughout the duration of the trial, in line with the TASC Good Clinical Practice Training Policy for Personnel Involved in Clinical Research.

13.3.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to trial staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee or Regulatory Authorities. The CI and trial staff involved with this trial will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

13.3.6 Data Protection

The CI and trial staff involved with this trial will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and trial staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Participant Confidentiality. Access to collated participant data will be restricted to the CI and appropriate trial staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13.3.7 Insurance and Indemnity

The University of Dundee and Tayside Health Board are Co-Sponsoring the trial.

Insurance. – The University of Dundee will obtain and hold Professional Negligence Clinical Trials Insurance cover for legal liabilities arising from the trial.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the trial].

Where the trial involves University of Dundee staff undertaking clinical research on NHS participants, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity. Co-Sponsors do not provide trial participants with indemnity in relation to participation in the Trial but have insurance for legal liability as described above.

14 TRIAL CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

The CI will seek Sponsor approval for any amendments to the Protocol or other trial documents. Amendments to the protocol or other trial docs will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC

and/or Regulatory Authority, as appropriate, and NHS R&D Office(s). Refer to TASC SOP 26 “Amendments to CTIMPs”

14.2 PROTOCOL DEVIATIONS, BREACHES AND WAIVERS

The CI will not implement any deviation from the protocol without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to trial participants.

In the event that the CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented in a TASC Deviation & Breach Log and notified to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, Regulatory Authority and local NHS R&D for review and approvals as appropriate. It is Sponsor policy that waivers to the Protocol will not be approved.

In the event that a serious breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the form “Notification to Sponsor of Potential Serious Breach or Serious Deviation”. Refer to TASC SOP 25 “Escalation and Notification of Serious Breaches of GCP or the Trial Protocol for CTIMPs”.

14.3 TRIAL RECORD RETENTION

Archiving of trial documents will be carried out as specified in TASC SOP 13: Archiving Clinical Research Data for Clinical Trials of Investigational Medicinal Products, (unless otherwise agreed with the Sponsor and by contract). As the data from this trial does not form part of an application for a Marketing Authorisation (MA) all trial documentation, including medical case notes, will be kept for at least 5 years.

14.4 END OF TRIAL

The end of trial is defined as last participant last visit (LPLV). The Sponsor and, CI have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, REC, Regulatory Authority and NHS R&D Office(s) within 90 days, or 15 days if the trial is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A final report of the trial will be provided to the Sponsor, REC and Regulatory Authority within 1 year of the end of the trial.

14.5 CONTINUATION OF DRUG FOLLOWING THE END OF TRIAL

This is not appropriate since confirmatory studies are necessary before guidelines for this condition would recommend this particular therapy.

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this trial resides with the trial team and their respective employers. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial report will be prepared.

15.2 PUBLICATION

The clinical trial report will be used for publication and presentation at scientific meetings. Trial investigators have the right to publish orally or in writing the results of the trial. Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

15.3 PEER REVIEW

This trial has been funded by the British Heart Foundation who have peer reviewed the grant application. Additional peer review of the protocol occurs via the Sponsorship Committee. Resulting publications will be reviewed by the referees of the journal to which the paper (and its protocol) will be submitted.

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17 APPENDIX 1: TRIAL SCHEDULE

Visit	Visit 1* Screening	Visit 2* Baseline/ Randomisation	Visit 3	Visit 4 (Tele Visit)	Visit 5	Two week wash-out period	Visit 6	Visit 7	Visit 8 (Tele Visit)	Visit 9 ****	Visit 10 (Final visit)
	Up to 4 weeks pre visit 2	**Day 0**	**Day 3** (+/-2 days)	**Week 3** (+/- 3 days)	**Week 6** (+/- 3 days)		**Week 9** (+/- 3 days)	**Week 9 + 3 days** (+/- 2 days)	**Week 12** (+/- 3 days)	**Week 15** (+/- 3 days)	**Week 19** (+/- 7 days)
Informed Consent	X										
Inc./Exc. Criteria	X	X									
PMH	X										
Demographics	X										
Clinical examination	X						X				X
Height	X										
Weight	X	X	X		X		X	X		X	X
Vital Signs – blood pressure & pulse	X	X	X		X		X	X		X	
Safety Bloods	X	X	X		X		X	X		X	
HbA1c	X				X		X			X	
Research Bloods		X	X		X		X	X		X	
Genetic Blood Sample		X									
Additional blood sample		X			X		X			X	
Urine sample	X	X	X		X		X	X		X	

Urine Pregnancy Test (WoCBP)	X	X	X		X		X	X		X	X
Ask if participant is pregnant (WoCBP)				X					X		
24 hour urinary collection			X		X			X		X	
Renal Physiology Test			X		X			X		X	
Drug Dispensing		X					X				
AE assessment		X	X	X	X		X	X	X	X	X
Record/Review Con Meds	X	X	X	X	X		X	X	X	X	X
Drug Compliance Check			X	X	X			X	X	X	

*Visits 1 and Visits 2 combined into one visit where participant is able to stay for results of safety blood tests.

Clinical examination: This will include examination for dehydration via examination of the cardiovascular system including capillary refill, jugular venous pressure and the presence/absence of oedema

Safety Blood sample: U&Es including bicarbonate, LFTs, Glucose, Magnesium, Calcium and Phosphate, Cholesterol, Urate and FBC

Research blood Sample: NT-proBNP, Cystatin C

Genetic Blood Sample: only to be taken if participant consent given.

Additional blood sample: for research purposes, will be stored anonymously for future research use for up to 10 years at the University of Dundee, only to be taken if participant consent given.

Urine sample: for protein/creatinine ration and albumin/creatinine ratio

24 hour urinary collection: Participant will complete this in the 24 hours before visit and bring to visit.

Renal Physiological test: described in Appendix 2

Visit 9**** - if the participant wishes to withdraw prematurely or at the PI's discretion, all trial procedures will be conducted as though the final visit, if participant agrees.

18 APPENDIX 2: TRIAL DAY TIMELINE

- 2 days pre-trial day: 2gram sodium and 2L/day controlled diet (food diary)
- 1 day: 24 urinary collection

Interval (minutes)	Urine		Blood	
- 30				Arrives fasted. 2 x cannula sited
- 15				15mls/kg oral water load over 15 minutes
0				
+ 30	Void urine. Water intake equal to urine volume.			
+ 60	Void urine. Water intake equal to urine volume			
+ 90	Void urine. Water intake equal to urine volume.			
+ 105		B1 (90-120 mins)	Bloods (serum B1) for U&Es & osmolality	
+ 120	Void urine. Water intake equal to urine volume. Collect urine (urine B1) for volume, sodium, creatinine & osmolality.			
+ 135		B2 (120-150 mins)	Bloods (serum B2) for U&Es & osmolality	
+ 150	Void urine. Water intake equal to urine volume. Collect urine (urine B2) for volume, sodium, creatinine & osmolality			IMP administered: Oral tablet (empagliflozin 25mg or placebo)

+ 165		D1 (150-180 mins)	Bloods (serum D1) for U&Es & osmolality	
+ 180	Void urine. Water intake equal to urine volume. Collect urine for volume, sodium, creatinine & osmolality			
+ 195		D2 (180-210 mins)	Bloods (serum D2) for U&Es & osmolality	
+ 210	Void urine. Water intake equal to urine volume. Collect urine for volume, sodium, creatinine & osmolality			IV Frusemide administered: half participant's screening dose
+ 225		F1 (210 – 240 mins)	Bloods (serum F1) for U&Es & osmolality	
+ 240	Void urine. Water intake equal to urine volume. Collect urine for volume, sodium, creatinine & osmolality			
+ 255		F2 (240-270 mins)	Bloods (serum F2) for U&Es & osmolality	
+ 270	Collect urine for volume, sodium, creatinine & osmolality.			**END OF STUDY PERIOD**