Objectives

Primary Objective:	**Outcome Measure:**
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the incidence of CV death or a HF event (hospitalisation for HF or equivalent HF event, i.e., an urgent HF visit)**.**	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF 3. An urgent HF visit

Secondary Objective:	**Outcome Measure :**
To compare the effect of dapagliflozin versus placebo on CV death or hospitalisation for HF.	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF
To compare the effect of dapagliflozin versus placebo on total number of recurrent HF hospitalisations and CV death.	Total number of recurrent HF hospitalisations and CV death.
To compare the effect of treatment with dapagliflozin versus placebo on the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score for HF symptoms and physical limitations.	Change from baseline measured at 8 months in the total symptom score of the KCCQ, a specific HF patient reported outcome questionnaire.

guidelines at the time of enrolment. To ensure stability, doses of evidence based HF medications (other than diuretics) can neither have been increased nor decreased for at least 4 weeks prior to inclusion in the study.

The study population will include patients both with and without T2D, as the beneficial hemodynamic effects appear to be independent of the glycaemic effect, and can therefore be expected in both groups. It was notable in EMPA-REG outcome study, studying the effect of empagliflozin that the reduction in CV death and HF was similar across baseline HbA1c subgroups, i.e., did not seem to be dependent on the level of baseline glycaemia. From published data we anticipate that approximately 40% of the HFrEF study population will have diabetes (Kristensen et al 2016). To ensure balance between the diabetic and non-diabetic cohorts, stratification will be employed, with inclusion of at least 30% of each of these cohorts.

The control group will receive placebo. All patients will be treated for their HFrEF according to local guidelines on standard of care treatment for HF.

1.2.2 Rationale for primary outcome measure

The main objective of the study is to investigate whether dapagliflozin, compared with placebo, reduces the incidence of CV death or hospitalisation for HF or equivalent event (i.e. an urgent HF visit) when added to background standard of care treatment. A HF event is defined as hospitalisation for worsening HF or an equivalent event (i.e., an urgent HF visit leading to an urgent, unplanned, assessment by a physician (e.g., in an Emergency Department) and requiring treatment for worsening heart failure (other than just an increase in oral diuretics), in accordance with the draft definition CDISC: Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials (Hicks et al 2014).

Acknowledging changing practice patterns and geographic variability in the use of hospitalisation in HF treatment, the more inclusive definition of "a heart failure event" is used. HF events consisting of both HF hospitalisations and urgent HF visits requiring urgent intensification of treatment (as described in the CDISC [Hicks et al 2014]) are components of the primary endpoint. Given the current financial pressures, particularly in the USA, to reduce HF hospitalisation, using the more traditional measure of HF hospitalisation only, risks missing a significant number of events.

The CDISC definitions of urgent HF visit are similar to those for heart failure hospitalisation (except that an increase in oral diuretic is not sufficient to qualify as a significant increase in HF therapy) and provide robust and objective criteria for accurately capturing true cases of worsening HF. The rationale for including outpatient urgent HF events, in addition to hospital admissions, is that it is the occurrence of worsening of the patient's condition necessitating treatment, and not the place of treatment, that is important. Importantly, episodes of worsening HF treated in the outpatient or emergency department setting are associated with an increased risk of subsequent death similar to that seen following a hospital admission (Okumura et al 2016).

1.2.3 Rationale for secondary outcome measure

The rationale for including CV death or hospitalisation for HF, but excluding non-hospitalised urgent HF visits, is that this is the more conventional composite HF endpoint, may be regarded as including "harder" outcomes and will allow direct comparison with other HF trials.

The rationale for including total number of hospitalisations (including re-hospitalisations) for HF is to capture the impact of recurrent non-fatal HF hospitalisations. Taken together with CV death, these events give a better estimate of the full burden of HF on patients and health-care systems than time-to-first event analysis. This outcome also provides a more detailed understanding of the potential treatment benefit in patients with chronic HF as it takes account of the effect of therapy on additional as well as first events.

While CV death and HF hospitalisations are clearly important to patients and health-care systems, the impact of HF on patients' symptoms and physical/social functioning is also important. In order to evaluate these aspects of the impact of HF, we will use the Kansas City Cardiomyopathy Questionnaire (KCCQ), a disease-specific patient reported outcomes (PRO) measure developed for patients with chronic HF. The KCCQ has shown to be a valid, reliable and responsive measure for patients with HF (Green et al 2000, Spertus et al 2005).

The rationale for the secondary renal composite endpoint is that renal dysfunction is very common in heart failure, may lead to discontinuation of disease-modifying therapies and is associated with poor outcomes. SGLT2 inhibition has previously shown beneficial effects on renal outcomes in patients with T2D and concurrent established cardiovascular disease (CVD) (

Wanner et al 2016) and if this effect was also found in HF it could be of considerable benefit. This potential renal benefit is simultaneously being evaluated in a separate study evaluating dapagliflozin treatment on renal outcomes in patients with chronic kidney disease (CKD).

All-cause mortality will be assessed as a secondary endpoint because it is important to evaluate the effect of dapagliflozin on non-cardiovascular, as well as cardiovascular, mortality and hence overall mortality.

1.2.4 Rationale for dose selection

The marketed dose (10 mg) of dapagliflozin has been demonstrated to be well tolerated and effective for the treatment of T2D but the efficacy on CV mortality and/or HF outcomes in patients with HF has not been evaluated. From a pharmacokinetic and pharmacodynamics perspective, 10 mg dapagliflozin is appropriate for use in patients with HF as this dose is expected to near maximally inhibit SGLT2 in the kidney. Also this dose was found to be well tolerated in a CKD stage 3 study (estimated glomerular filtration rate (eGFR) 30 to 60 mL/min/1.73m^2) (Kohan et al 2014). In addition to the preferred 10 mg dose, the marketed 5 mg dose of dapagliflozin may be used in the study when clinically indicated, however, it is expected to provide less inhibition of renal SGLT2 and thus exert less pharmacodynamics effects, see Section 3.9.1, for details.

1.3 Benefit/risk and ethical assessment

Dapagliflozin has global market approval and based on global cumulative sale figures up to March 2016 it is estimated that dapagliflozin has been administered for >1 000 000 patient years.

1.3.1 Potential risks

Details regarding potential risks associated with administration of dapagliflozin once daily are provided in the Investigator's Brochure (IB). Additional considerations relevant for the target population are described below.

Dapagliflozin has not been shown to induce hypoglycaemia in non-diabetes patients. In clinical pharmacology studies, healthy subjects have been treated with single oral doses up to 500 mg and multiple oral doses of 100 mg up to 14 days without any hypoglycaemic events.

Events related to volume depletion (including reports of dehydration, hypovolemia, or hypotension) and events related to changes in renal function have been thoroughly evaluated in the dapagliflozin phase III program. In a large pool consisting of 21 active- and placebo-controlled studies, serious adverse events (SAEs) of volume depletion were infrequently reported and the proportion was lower for patients treated with dapagliflozin than control (0.1% versus 0.2%). SAEs of renal impairment/failure were also rarely reported and balanced between treatment groups in the clinical trial program. Nine (0.2%) SAEs were reported in the dapagliflozin group and 5 (0.1%) SAEs were reported in the control group.

In a recent analysis of patients with pre-existing HF using pooled data from previous dapagliflozin studies (Kosiborod et al 2016), the rate of hypovolemic events was similar between dapagliflozin and placebo.

Although the phase III data in patients with CKD 3 show an increased frequency of overall renal events in patients treated with dapagliflozin as compared with placebo, most of these events have been related to laboratory detected transient increases in creatinine.

In an analysis using pooled data on a subset of patients with CKD 3, micro or macro albuminuria and treatment with angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARB) there was no meaningful difference between dapagliflozin and placebo in terms of SAEs of renal impairment/failure or SAEs of volume depletion (Sjöström et al 2015).

Loop-diuretics are widely used in the target patient population and are also allowed in this study. In the dapagliflozin phase III program, patients using loop diuretics were more likely to have an event related to volume depletion regardless of whether they were treated with dapagliflozin or placebo. During the short-term period a pooled analysis showed 6 (2.5%) subjects with events in patients on dapagliflozin 10 mg and 4 (1.5%) in patients on placebo. When including the long-term extension periods of the phase III trials in the analysis, the corresponding values were 7 (3.0%) versus 7 (2.7%) for dapagliflozin and placebo, respectively.

10 mg versus placebo, given once daily in addition to background standard of care therapy, for the prevention of CV death or reduction of HF events.

It is estimated that approximately 7000 patients at approximately 500-600 sites in 20-25 countries will be enrolled to reach the target of approximately 4500 randomised patients. The investigational product (IP) will be added to the prescribed background therapy for HF (and background therapy for T2D when applicable) as considered appropriate by the investigator and in accordance with regional standards of care.

The anticipated duration of the study is approximately 33 months. The study closure procedures will be initiated when the predetermined number of primary endpoints is predicted to have occurred (n=844), i.e., the study end date (SED) (see Figure 1). The study duration may be changed if the event rate or randomisation rate is different than anticipated. The study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the DMC review.

An echocardiographic sub-study is planned to be conducted in a subset of patients (approx. 300-400 patients) in the Dapa-HF trial. The sub-study is designed to evaluate the impact of dapagliflozin at a dose of 10 mg daily, compared to placebo, in addition to conventional heart failure treatment, on changes in cardiac structure and function as determined by echocardiography.

To determine if dapagliflozin compared with placebo reduces the incidence of a composite endpoint of worsening renal function.	Time to the first occurrence of any of the components of this composite: 1. ≥50% sustained* decline in eGFR 2. Reaching End Stage Renal Disease (ESRD) – Sustained* eGFR <15 ml/min/1.73m^2 or, – Chronic* dialysis treatment or, – Receiving a renal transplant 3. Renal death **As defined in the Clinical Event Adjudication (CEA) charter*
To determine whether dapagliflozin, compared with placebo, reduces the incidence of all-cause mortality.	Time to death from any cause.

2.3 Safety objectives

Safety Objective:	**Outcome Measure :**
To evaluate the safety and tolerability of dapagliflozin in this patient population.	1. Serious Adverse Events (SAEs) 2. Discontinuation of IP due to Adverse Events (DAEs) 3. Changes in clinical chemistry/haematology parameters 4. AEs of interest (volume depletion, renal events, major hypoglycaemic events, fractures, Diabetic ketoacidosis (DKA), AEs leading to amputation and AEs leading to a risk for lower limb amputations [“preceding events”])

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure :
To compare the effect of dapagliflozin versus placebo on an expanded composite outcome reflecting worsening of HF.	Time to the first occurrence of any of the components of the expanded composite worsening HF outcome: 1. CV death 2. Hospitalisation for HF 3. An urgent HF visit 4. Documented evidence of worsening HF symptoms/signs leading to initiation of a new treatment for HF sustained for at least 4 weeks or augmentation of existing oral therapy for HF (eg, increase in dose of diuretic) sustained for at least 4 weeks.
To determine whether dapagliflozin compared with placebo will have effect on New York Heart Association (NYHA) class.	Change in NYHA class from baseline.
To determine whether dapagliflozin compared with placebo will reduce the incidence of diagnosis of atrial fibrillation (AF) in patients without history of AF at baseline.	Proportion of patients without history of AF at baseline with a new diagnosis of AF during the study.
To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of hyper – and hypokalaemia.	Time to the first occurrence of each of any of the following central lab levels of serum potassium: • >6.0 mmol/L • >5.5 mmol/L • <3.5 mmol/L • <3.0 mmol/L
To determine whether dapagliflozin compared with placebo will affect the number of events of doubling of serum creatinine.	Number of events with doubling of serum creatinine (compared with the most recent laboratory measurement).
To determine whether dapagliflozin compared with placebo will reduce the incidence of diagnosis of T2D in patients without diabetes at baseline.	Proportion of patients without T2D at baseline with a new diagnosis of T2D during the study.
To determine whether dapagliflozin compared with placebo will have effect on HbA1c in T2D subgroup.	Changes in HbA1c from baseline.
To determine whether dapagliflozin compared with placebo will have an effect on systolic BP.	Change in systolic BP from baseline.

To determine whether dapagliflozin compared with placebo will have an effect on body weight.	Change in body weight from baseline.
To determine whether dapagliflozin compared with placebo will reduce the incidence of myocardial infarction (MI).	Time to first fatal or non-fatal MI.
To determine whether dapagliflozin compared with placebo will reduce the incidence of any stroke (ischemic, haemorrhagic, or undetermined).	Time to first fatal or non-fatal stroke of any cause.
To compare the effect of dapagliflozin versus placebo on health status assessed by Patient Global Impression of Change (PGIC) and Patient global impression of severity (PGIS) questionnaires.	Changes in health status measured by PGIC and PGIS.
To compare the effect of dapagliflozin versus placebo on health status assessed by EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment.	Changes in health status measured by EQ-5D-5L.
To collect and analyse pharmacokinetic (PK) samples for dapagliflozin concentration.	Not applicable. Results will be reported separately.
To assess cardiac structure and function with echocardiography at baseline and 8 months follow-up.	Not applicable. Results will be reported separately.
To collect and store samples of plasma and serum for future exploratory biomarker research.	Not applicable. Results will be reported separately.

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of signed informed consent prior to any study specific procedures

2. Male or female, aged ≥18 years at the time of consent

Essential treatments

Essential disease modifying/evidence based treatments such as ACE-I or ARBs or sacubitril/valsartan, mineralocorticoid receptor antagonists and beta-blockers for patients with HF, should NOT be reduced in dose or discontinued unless all other measures fail to improve the patient's situation. In the setting of acute worsening of HF or other acute situations it may be acceptable to interrupt treatment on a temporary basis in certain circumstances (eg, an ACE-I/ARB if the patient has experienced a significant deterioration in renal function, a beta-blocker if the patient is unduly bradycardic or hypotensive, an MRA if the patient has hyperkalaemia).

Patients at risk of volume depletion

Temporary interruption of IP may be considered in patients thought to be at risk of volume depletion/hypotension, such as patients with an acute medical illness potentially causing volume depletion because of inadequate fluid intake or fluid/blood loss (e.g., gastroenteritis, gastrointestinal haemorrhage), or those undergoing major surgery.

3.9.2 Investigational product (IP) restart or dose increase from dapagliflozin 5 mg to 10 mg or matching placebo

Restart of randomised IP is always encouraged. Whenever possible, randomised IP should be restarted if stopped or the dose increased if previously reduced. Even if a premature treatment discontinuation visit (PTDV) was completed due to discontinuation of IP, this should not prevent the patient to return to randomised IP if deemed appropriate.

Every attempt should be made to maintain patients on dapagliflozin 10 mg or matching placebo during the course of the study. If the dose has been decreased to 5 mg or interrupted, the dose should be increased back to dapagliflozin 10 mg or matching placebo or re-introduced as soon as, in the opinion of the investigator, the patient's condition is stable.

3.9.3 Procedures for discontinuation of a patient from investigational product (IP)

At any time, patients are free to discontinue IP. A patient that decides to discontinue will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by an investigator. Adverse events will be followed up, see Section 6, and all IP should be returned by the patient.

Generally AEs, SAEs and potential endpoint events should not lead to IP discontinuation, unless there is a clear clinical rationale to do so.

Discontinuation from IP is not the same as complete withdrawal from the study. If a patient is completely withdrawn from study, see Section 3.10.2.

- Potential renal endpoints:
  - Dialysis
  - Kidney transplantations
  - Doubling of serum creatinine (since the most recent central laboratory measurement)
- Cardiac ischaemic events (MI and unstable angina)
- Cerebrovascular events (stroke and TIA)
- DKA (not considered an efficacy variable but will be adjudicated as a safety variable)

In addition, eGFR declines ≥50% from baseline, eGFR values <15 mL/min/1.73m^2, new diagnosis of atrial fibrillation and new diagnosis T2D will be recorded in the eCRF but will not be adjudicated.

For each potential endpoint event, the investigator or delegate will record information in the eCRF. If the event is subject to adjudication, relevant source documents will be assembled. The source documents and relevant eCRF data will be sent for central adjudication.

Detailed instructions regarding endpoint reporting will be provided to the study sites.

Additional details about the evaluations of potential endpoint events will be described in the CEA charter.

5.1.2 Classification of Death

The CEA committee members will adjudicate and classify all deaths based on definitions described in the CEA charter. For the purpose of the efficacy analysis, deaths will be sub-classified by CV and non-CV as well as renal primary cause (death due to ESRD when dialysis is not given). The investigator will record the classification of death as CV or Non-CV death in the eCRF.

5.1.3 Heart failure (HF) events

All potential HF endpoint events (hospitalisations for HF or urgent HF visits) should be recorded as an AE and on a separate page in the eCRF and submitted to the CEA for adjudication. The CEA will adjudicate the events as specified in the CEA Charter.

See for definition of Heart failure event according to CDISC definition (Hicks et al 2014) which is currently the latest version. CDISC may be updated during the course of the study. The CEA charter will describe in detail how HF events will be adjudicated in the current study.

5.1.4 Potential renal endpoints

5.1.4.1 Endpoints related to eGFR decline

eGFR baseline is defined as the mean central laboratory value from Visit 1 and Visit 2.

Laboratory values related to eGFR decline will trigger an action by site in the following situations:

- **Potential Renal Endpoints Local laboratory** values indicate that eGFR value has declined ≥50% compared with baseline, or is below 15 mL/min/1.73m^2.

  NB As soon as possible, patient should come to the study site for confirmation by a central laboratory testing.

  OR

- **Central laboratory** values, collected during a study visit, indicating that eGFR value has declined ≥50% compared with baseline, or is below 15 mL/min/1.73m^2.

The central laboratory will notify site if eGFR is <15 mL/min/1.73m^2 or if there is ≥50% decline in eGFR compared to baseline. A re-sampling should be done after at least 4 weeks, and preferably no later than 6 weeks after the first sampling. If the eGFR decline is confirmed, it should be recorded in the eCRF.

The central laboratory will calculate eGFR using CKD-EPI equation (Levey at al 2009).

5.1.4.2 Dialysis and renal transplantation

If a patient starts dialysis and or go through a renal transplantation this will be recorded in the eCRF and submitted for adjudication.

5.1.4.3 Doubling of serum creatinine

Doubling of serum creatinine (compared to the most recent central laboratory measurement) will be recorded in the eCRF and submitted for adjudication.

Recording of doubling of serum creatinine compared to the most recent central laboratory result can be triggered by a local laboratory result OR a central laboratory result.

5.1.5 Initiation of new, or increased dose of existing oral treatment for worsening of heart failure (HF)

Documented evidence of worsening HF symptoms/signs leading to initiation of a new treatment for HF sustained for at least 4 weeks or augmentation of existing oral therapy for HF (e.g., increase in dose of diuretic) sustained for at least 4 weeks, will be reported in the eCRF.

5.1.6 New York Heart Association (NYHA) class

The definition of NYHA class is included in Appendix D. The investigator will evaluate this according to the study plan and assessment will be recorded in the eCRF.

5.1.7 New diagnosis of Atrial Fibrillation (AF)

New diagnosis of AF during the study will be defined as proportion of patients, without history of AF at baseline, who develop AF during the study. This will be recorded as an AE with additional information on a separate eCRF page.

5.1.8 New diagnosis of type 2 diabetes

New onset of T2D, post randomisation, defined according to the following criteria:

- Reporting of new onset T2D necessitating initiation of anti-diabetic medication.

  OR

- HbA1c $\geq$6.5% (48 mmol/mol) measured by central lab at two consecutive study visits.

New onset of T2D will be recorded as an AE and on a separate eCRF page.

5.1.9 Cardiac ischaemic events

Sites should record potential acute coronary syndromes such as MI and unstable angina in the eCRF and submit for adjudication. The CEA committee members will adjudicate all potential cardiac ischaemic events to decide if they qualify as MI according to the criteria defined in the CEA charter.

5.1.10 Cerebrovascular (CV) events

Sites should record potential strokes and TIAs in the eCRF and submit to the CEA for adjudication. The CEA committee members will adjudicate all cerebrovascular events to decide if they qualify as stroke according to the criteria defined in the CEA charter.

5.1.11 Patient reported outcomes (PROs)

PROs is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become important endpoints for regulatory and reimbursement authorities when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered in the study: PGIS, PGIC, KCCQ, EQ-5D-5L (see Appendix E). Patients will be asked to complete the PROs at the visits as specified in Table 1.

5.1.11.1 Patient global impression of severity (PGIS)

The PGIS question captures patient's severity of HF symptoms. It will be used as an anchor in the estimation of the minimal important change.

5.1.11.2 Patient global impression of change (PGIC)

The PGIC question will be used to capture patients overall change in HF symptoms since start of the treatment. It will also be used as an anchor in the estimation of the minimal important change.

5.1.11.3 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a self-administered disease specific instrument and has shown to be a valid, reliable and responsive measure for patients with HF (Green et al 2000, Spertus et al 2005). The KCCQ consists of 23 items measuring HF-related symptoms, physical limitations, social limitations, self-efficacy, and health-related quality of life. The total symptom score incorporates the symptom domains into a single score. Scores are transformed to a range of 0-100. Higher scores represent a better outcome.

5.1.11.4 EuroQol five-dimensional five-level questionnaire (EQ-5D-5L)

The EQ-5D-5L is a self-reported questionnaire that is used to derive a standardized measure of health status, also referred to as a utility score. EQ-5D-5L utility scores are widely accepted by reimbursement authorities and will be used to support health economic evaluations.

5.1.11.5 Administration of patient reported outcomes (PRO)

All PROs will be administered electronically (ePRO). Patients will complete the PRO assessments at the study site using a handheld electronic device (ePRO). Each site must allocate the responsibility for the administration of the ePROs to a specific individual and, if possible, assign a backup person to cover if that individual is absent.

All assessments should be completed as follows:

- Patient must not receive help from relatives, friends, or site personnel to answer or clarify the PRO questionnaires in order to avoid bias. If a patient uses visual aids (e.g., spectacles or contact lenses) for reading and does not have them at hand, the patient will be exempted from completing the PROs questionnaires on that visit.
- Before any other study procedures are conducted at a given visit.
- Before being seen by the investigator.
- PRO questionnaires must be completed by the patient in private.
- The appointed site personnel should explain to patient the value and relevance of ePRO assessments and inform them that these questions are being asked to find out, directly from patients, how they feel. The appointed site personnel should also stress that the information is confidential.

- The appointed site personnel must show patients how to use the ePRO device, in accordance with the instructions provided.
- The appointed site personnel should remind patients that there are no right or wrong answers, and the patient should be given sufficient time to complete the PRO questionnaires at his/her own speed.
- If the patient is unable to read the questionnaire (e.g., is blind or illiterate), the patient will be exempted from completing the PRO questionnaires and may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site personnel.

5.2 Safety assessments

5.2.1 Laboratory assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in Table 2. The date of central laboratory sample collection will be recorded in the eCRF. All laboratory variables will be analysed at the central laboratory, except urine human chorionic gonadotropin (hCG) (pregnancy test, using a dipstick provided by the central laboratory), and optional local laboratory samples taken at enrolment, which will be analysed locally.

All samples should be taken by adequately trained study personnel and handled in accordance with instructions in the Laboratory Manual. Up to date reference ranges will be provided during the study and laboratory results will be compared with the laboratory standard normal ranges and reported back to site.

Samples sent to the central laboratory will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

The following safety laboratory variables will be measured:

Table 2 Laboratory variables

Haematology	**Clinical Chemistry**
Haemoglobin (Hb) [b]	Alanine transaminase (ALT) [b]
Haematocrit	Alkaline phosphatase (ALP) [b]
	Aspartate transaminase (AST) [b]
Urinalysis (dipstick)	Bilirubin, total[b]
U-hCG (pregnancy test) [e]	Blood urea nitrogen (BUN) [a]
	Creatinine (including eGFR assessment) [a]
	HbA1c[a]
	NT-proBNP[c]

	Phosphate[d]
	Potassium[a]
	Sodium[a]

[a] Central laboratory analysis at all on site visits.
[b] Central laboratory analysis at visit 1, PTDV and SCV.
[c] Central laboratory analysis at visit 1, 2 and 6.
[d] Central laboratory analysis at visit 2, 5, PTDV and SCV.
[e] Local dipstick analysis at visit 1 and visit 2.

The investigator should make an assessment of the laboratory results with regards to clinically relevant abnormalities. The laboratory results should be signed, dated and retained at the site as source data for laboratory variables.

5.2.1.1 Unscheduled laboratory assessments

Unscheduled laboratory samples will be requested by the central laboratory for follow-up on e.g., eGFR values. Follow-up samples related to eGFR should be collected during an unscheduled visit and sent to central laboratory for analysis.

5.2.2 Physical examination

A general physical examination will be performed at the time of randomization and when the patient stops IP and include an assessment of the following: general appearance, respiratory and cardiovascular systems (including oedema) and abdomen.

A targeted physical examination (including heart, lungs, oedema, dyspnoea, ascites, and weight gain) will be performed at onsite visits where no general physical examination is being performed, (see Table 1) with focus on signs for HF and volume status.

The assessment dates will be recorded in the eCRF.

5.2.3 Electrocardiogram (ECG)

A 12-lead ECG (standard ECG with a paper speed of 25-50 mm/second covering at least 6 sequential beats) will be recorded at enrolment (Visit 1) after the patient has been lying down to rest for at least 5 minutes. ECG date, heart rate and heart rhythm will be recorded in the eCRF. The baseline ECG should be made available for CEA upon request, to facilitate adjudication of potential cardiac ischaemic events and events with new onset of AF.

5.2.4 Vital signs

Vital signs will be assessed according to the study plan, Table 1.

5.2.4.1 Pulse and blood pressure (BP)

Pulse and BP will be measured three times at all visits, and all measurements will be recorded in the eCRF. The measurements should be done before any blood sampling using a

standardized cuff adapted to the size of the patient's arm after the patient has been sitting and resting for least 5 minutes. Preferably, the same arm should be used at all visits.

5.2.4.2 Body weight and height

The patient's body weight will be measured with light clothing and no shoes at all visits. If the patient has a prosthetic limb, this should be consistently worn or not worn during all weight measurements. The patient's height will be measured at visit 1, with no shoes. The weight and height will be recorded in the eCRF.

5.3 Other assessments (Not applicable)

5.4 Pharmacokinetics (PK)

5.4.1 Collection of samples

One pre-dose blood sample for determination of the dapagliflozin concentration in plasma will be taken at visit 7. Information about last intake of IP and sampling ID, date and time will be recorded in the eCRF.

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

5.4.2 Determination of drug concentration

Samples for determination of dapagliflozin concentration in plasma will be analysed by the bioanalytical laboratory on behalf of AstraZeneca, using an appropriate validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.3 Storage and destruction of pharmacokinetic samples

PK samples will be analysed during the course of the study and disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier). The results of the PK analyses will be kept at the bioanalytical laboratory until the end of the study to prevent unblinding.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

5.5 Pharmacodynamics (Not applicable)

5.6 Pharmacogenetics (Not applicable)

5.7 Biomarker analysis

Serum and plasma will be collected and stored for potential future analysis for exploratory biomarkers to assess correlations with the activity of the diseases affecting patients in the study, effects of study drug, clinical outcomes and toxicity.

It is mandatory to obtain the patient's consent to the donation and use of biological samples. The consent date will be recorded in the eCRF. Patients not consenting to donate biological samples for future biomarker analysis are still able to participate in the study, but without providing samples for biomarker analysis.

The biomarkers to be studied will be selected on possible relevance on pathophysiology of the studied diseases.

5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored in AZ biobank for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with dapagliflozin to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

The Principal Investigator (PI) ensures that samples are collected, labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AZ and appropriate labelling, shipment and containment provisions are approved. Samples can be shipped to specialist labs around the world and analysed by academic collaborators or commercial partners.

5.7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The PI at each site keeps full traceability of collected biological samples from the patients while in storage at the study site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from randomisation (Visit 2) throughout the treatment period until and including the patient's last visit.

SAEs will be recorded from the time of informed consent throughout the treatment period until and including the patient's last visit.

AEs should be recorded in the eCRF only if:

- **It qualifies as an SAE** (as defined in Section 6.2)
- The AE is the reason for permanent discontinuation from IP (**DAE**)
- The AE is the reason for **IP interruption** or **dose reduction**
- It qualifies as an **AE of interest**:
  - Volume depletion
  - Renal events
  - Major hypoglycaemic events
  - Fractures
  - Potential DKAs
  - AEs leading to amputation and AEs leading to a risk for lower limb amputations ("preceding events")
  - A potential endpoint (see Section 5.1) that fulfils the AE criteria. NB: not all potential endpoints are per definition an AE, e.g. a potential endpoint solely related to laboratory findings (see Section 6.3.5) should not be recorded unless any of the above mentioned criteria is met.

An AE/SAE could be associated with more than one potential endpoint. In such scenario, only one AE/SAE should be reported but all potential endpoints should be reported individually.

6.3.2 Adverse events of interest

6.3.2.1 Volume depletion

Events of volume depletion (e.g., dehydration, hypovolemia, or hypotension) will be recorded in the eCRF as AEs.

6.3.2.2 Renal events

Renal events, such as an acute clinically relevant decline in kidney function as judged by the investigator, will be recorded in the eCRF as AEs. If the event also qualifies as a potential endpoint as defined in Section 5.1.4, a separate eCRF will also be completed.

6.3.2.3 Major hypoglycaemic event

A major hypoglycaemic event is defined as an event that requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.

Plasma glucose concentrations may not be available during an event, but neurological recovery following the corrective actions is considered sufficient evidence that the event was induced by a low plasma glucose concentration. Major hypoglycaemic episodes will be recorded in the eCRF as an AE and on an additional eCRF page.

6.3.2.4 Fractures

All fractures will be recorded in the eCRF as AEs.

6.3.2.5 Diabetic ketoacidosis (DKA)

All potential events of DKA will be recorded in the eCRF and submitted to an independent DKA Adjudication Committee, see Section 6.8.5.

6.3.2.6 Adverse events (AEs) leading to amputation and AEs leading to a risk for lower limb amputations ("preceding events")

To ensure that data on amputations is systematically collected, amputations and underlying conditions will be recorded on a specific eCRF page. The adverse event leading to amputation should be recorded in the eCRF as AE/SAE.

In addition, non-serious and serious AEs putting the patient at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as AE/SAE whether or not it is leading to an amputation. The lower limb "preceding events" of interest are vascular, diabetic foot related, wounds, infections and neuropathies for which additional information will be collected (for details see eCRF instruction).

6.3.1 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.2 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity (mild/moderate/severe)
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s) and/or other medication
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria described in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

calendar day of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AE where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative. If the WBDC system is not available, then the investigator or other site personnel reports a SAE to the appropriate AstraZeneca representative by telephone in accordance with SAE reporting timelines.

The AstraZeneca representative will advise the investigator/site personnel how to proceed.

6.4.1 Reporting of SAEs considered to be potential endpoints

In order to avoid unnecessary unblinding of efficacy endpoint events, certain SAEs which are also potential endpoints (i.e., fatal AEs and HF events) will not be reported to health authorities Clinical data for the above mentioned events will be recorded as AEs/SAEs as well as on separate event forms in the eCRF. Recording of a suspected endpoint should be done within the same timeframes as defined for SAEs (see Section 6.4).

In addition, fatal AEs and potential HF endpoints will be centrally adjudicated by an independent CEA committee (see Section 5.1.1 and 6.8.4). If adjudication confirms the endpoint, the SAE will not be reported to health authorities. However, if it is determined by the CEA committee that a potential endpoint does not meet the endpoint criteria, the event will be reported (according to the timelines specified in Section 6.4) to AZ patient safety data entry site and if applicable to the health authorities (note that the clock starts when the adjudication results are available).

6.5 Overdose

Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with T2D. Suspected single intake of more than 50 tablets of 10 mg dapagliflozin tablets or repeated intake of more than 10 tablets of 10 mg dapagliflozin tablets should be reported on the eCRF overdose module. If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

For further information regarding overdose, refer to the IB.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module

- An overdose without associated symptoms is only recorded on the Overdose eCRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the investigator or other site personnel inform appropriate AZ representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AZ.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the course of the study, then the investigator or other site personnel informs the appropriate AZ representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT paper CRF form is used to report the outcome of the pregnancy.

6.8.5 Diabetic Ketoacidosis Adjudication Committee T2D

All potential events of DKA will be submitted to an independent DKA Adjudication Committee. The committee will be kept blinded to the treatment codes. A separate DKA Adjudication Manual will define and describe the procedures for the collection of DKA information, handling, adjudication criteria and reporting of these events.

6.9 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IxRS errors)
- Wrong drug administered to subject (excluding IxRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IxRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging

8.3.2 Safety analysis set

All patients who received at least 1 dose of randomised treatment will be included in the safety population. Patients will be analysed according to the treatment actually received. The Safety analysis set will be considered the primary analysis set for all safety variables.

8.4 Outcome measures for analyses

8.4.1 Primary outcome measure

The primary outcome measures are detailed in Section 2.1.

8.4.2 Secondary outcome measure

The secondary outcome measures are detailed in Section 2.2.

8.4.3 Safety outcome measure

The safety outcome measures are detailed in Section 2.3.

8.4.4 Exploratory outcome measure

The exploratory outcome measures are detailed in Section 2.4.

8.5 Methods for statistical analyses

8.5.1 Hypotheses

The Type I error rate for the analysis of the primary endpoint will be adjusted for the interim analyses performed by the DMC.

For the primary endpoint the following hypothesis will be tested at the 2.496% 1-sided level:

H_0: HR [dapagliflozin:placebo] ≥ 1

Versus

H_1: HR [dapagliflozin:placebo] < 1

8.5.2 Closed testing procedure

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilized. The Type I error will be controlled at a one-sided 0.02496 level for multiplicity across primary and secondary endpoints and in consideration of planned interim analyses. Statistical significance will be assessed in the pre-specified order of the endpoints as specified in Section 2.1 and 2.2. The testing procedure will continue down the hierarchy if the preceding endpoint is rejected at a one-sided 0.02496 level and will stop if the preceding endpoint is not rejected at a one-sided 0.02496 level. Exploratory endpoints will be tested at a one-sided 0.025 level without adjustment for multiplicity.

8.5.3 Analysis of the primary variable(s)

The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the ITT principle using the FAS, using events adjudicated and confirmed by CEA.

In the analysis of the primary composite endpoint, treatments (dapagliflozin versus placebo) will be compared using a Cox proportional hazards model with a factor for treatment group, stratified by T2D status at randomisation, and adjusting for history of hospitalisation for heart failure. In general, the analysis will use each patient's last contact as the censoring date for patients without any primary events. The p-value, HR and 95% confidence interval will be reported.

The contribution of each component of the primary composite endpoint to the overall treatment effect will be examined. Methods similar to those described for the primary analysis will be used to separately analyze the time from randomisation to the first occurrence of each component of the primary composite endpoint. Last contact will be treated as the censoring date for patients without the endpoint of interest. HR and 95% confidence intervals will be reported.

Kaplan-Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoint will be calculated and plotted, for overall analysis and for the individual components.

8.5.4 Analysis of the secondary variable(s)

The time-to-event secondary variables will be analysed in the similar manner as the primary variable, including time to the first occurrence of hospitalisation for HF or CV death, time to the first occurrence of any of the components of the renal composite endpoint, and time to death from any cause.

A composite outcome of all HF hospitalisations (first and recurring) and CV death will be analysed by the semi-parametric proportional rates model (Lin et al 2000) to test the treatment effect and to quantify the treatment difference. Other analysis methods may also be considered.

Change from baseline to each visit for KCCQ will be analysed with a repeated measures method. This model will be used to assess the time point of 8 months, although summaries at all visits will also be presented. A responder analysis, where a response is defined as a clinically meaningful change of 5 or more points of the Total Symptom Score, will also be performed.

8.5.5 Subgroup analysis

Subgroup variables for the primary efficacy endpoint and secondary efficacy endpoints include demography, baseline disease characteristics, baseline concomitant medications and others. Cox proportional hazard model, the semi-parametric proportional rates model, or the repeated measures model will be performed to examine treatment effects within relevant

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AZ will handle the distribution of any of these documents to the national regulatory authorities.

AZ will provide Regulatory Authorities, IRB/IECs and Principal Investigators with safety updates/reports according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the incidence of CV death or a HF event (hospitalisation for HF or equivalent HF event, i.e., an urgent HF visit)**.**	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF 3. An urgent HF visit

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure :**
To compare the effect of dapagliflozin versus placebo on CV death or hospitalisation for HF.	Time to the first occurrence of either of the components of this composite: 1. CV death 2. Hospitalisation for HF
To compare the effect of dapagliflozin versus placebo on total number of recurrent HF hospitalisations and CV death.	Total number of (first and recurrent) HF hospitalisations and CV death.
To compare the effect of treatment with dapagliflozin versus placebo on the KCCQ total symptom score for HF symptoms and physical limitations.	Change from baseline measured at 8 months in the total symptom score of the KCCQ, a specific HF patient reported outcome questionnaire.

E2 Patient Global Impression of Change (PGIC) for Heart Failure Symptoms

Patient Global Impression of Change for Heart Failure Symptoms

Overall, how would you rate the change in your heart failure symptoms since starting this study?

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

Secondary Objective:	**Outcome Measure :**
To determine if dapagliflozin compared with placebo reduces the incidence of a worsening renal function composite outcome.	Time to the first occurrence of any of the components of this composite: 1. ≥50% sustained* decline in estimated glomerular filtration rate (eGFR) 2. Reaching End Stage Renal Disease – Sustained* eGFR <15 ml/min/1.73m^2 or, – Chronic* dialysis treatment or, – Receiving a renal transplant 3. Renal death **As defined in the Clinical Event Adjudication (CEA) charter*
To determine whether dapagliflozin, compared with placebo, reduces the incidence of all-cause mortality.	Time to death from any cause.

Safety Objective:	**Outcome Measure :**
To evaluate the safety and tolerability of dapagliflozin in this patient population.	1. Serious Adverse Events (SAEs) 2. Discontinuation of Investigational Product (IP) due to Adverse Events (DAEs) 3. Changes in clinical chemistry/haematology parameters 4. AEs of interest (volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis, AEs leading to amputation and AEs leading to a risk for lower limb amputations [“preceding events”])

Furthermore, other post hoc safety analyses of importance to the current target population have not identified any indication of an increased risk of marked abnormalities in potassium levels (≥ 6mmol/L) in either patients with CKD 3 and ACE-I/ARB treatment (Sjöström et al 2015) or in patients on concomitant treatment with potassium sparing agents (Kosiborod et al 2016).

1.3.1.1 Protection against risks

This study has been designed with appropriate measures in place to monitor and minimize any potential health risks to participating patients. In order to ensure the safety of all patients participating in AstraZeneca sponsored studies, reviews of all safety information from all ongoing clinical dapagliflozin studies are conducted as they become available. In addition, an independent Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of the patients by reviewing safety data throughout the study.

1.3.2 Potential benefits to patients

All HF patients in the study will be optimally treated according to standard of care and dapagliflozin or placebo will be administered on top of this treatment. The hypothesis is that dapagliflozin will reduce CV mortality or hospitalisation of HF or equivalent event in patients randomised to active drug. Dapagliflozin is also known to decrease body weight (or prevent weight gain) as well as lower BP and is believed to be nephroprotective through non-glycaemic mechanisms.

All patients participating in clinical trials irrespective of whether treated with active treatment or not, generally receive closer medical attention than those in ordinary clinical practice which may be to their advantage.

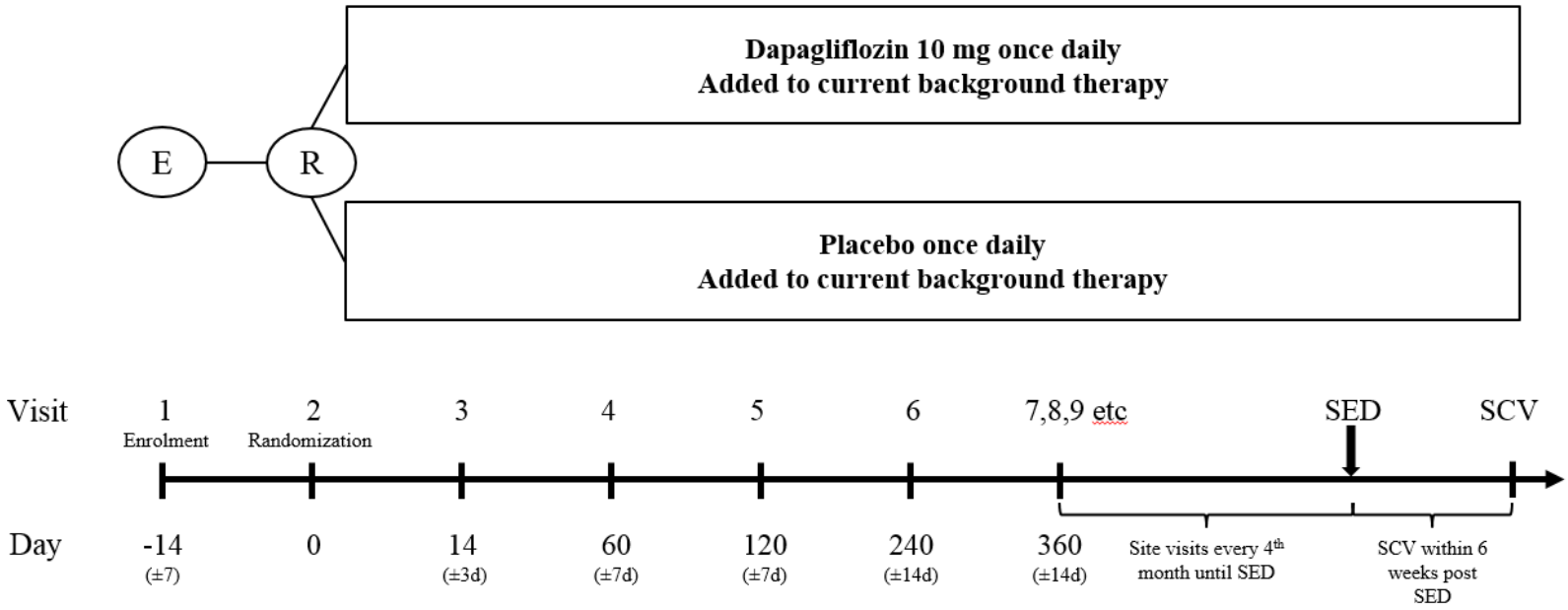
1.3.3 Conclusion

Considering the non-clinical and clinical experience with dapagliflozin and the precautions included in the study protocol, participation in this study should present a minimal and thus acceptable risk to patients who meet the inclusion/exclusion criteria and consent to take part in the study. At the time of writing this clinical study protocol, no available SGLT2 inhibitor is indicated for HF risk reduction in patients with HFrEF. The Phase IIb/III program in T2D has established the efficacy and safety of dapagliflozin in lowering glucose (as assessed by HbA1c). Another SGLT2 inhibitor, empagliflozin, has demonstrated reduction in HF hospitalisation and CV mortality in patients with T2D and CVD (Zinman et al 2015). The dapagliflozin programme has also provided hypothesis-generating data suggesting lower incidence of hospitalisation for HF with dapagliflozin treatment. This clinical study will test this hypothesis in a rigorous fashion. The potential results could offer substantial benefit to patients with HFrEF.

1.4 Study Design

This is an international, multicentre, parallel group, event-driven, randomised, double-blind, placebo-controlled study in patients with chronic HFrEF, evaluating the effect of dapagliflozin

Figure 1 ***Study flow chart***



SED = Study end date (ie, date when the predetermined number of adjudicated primary events is predicted to have occurred)
E = enrolment
SCV = Study closure visit
R = Randomization

3. Established documented diagnosis of symptomatic HFrEF (New York Heart Association (NYHA) functional class II-IV), which has been present for at least 2 months and is optimally treated with pharmacological and/or device therapy, as indicated

   NB: Patients in which additional pharmacological or device therapy is contemplated, or should be considered, must not be enrolled until therapy has been optimized and is stable for ≥1 month.

4. Left ventricular ejection fraction (LVEF) ≤40% (echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI) within the last 12 months prior to enrolment (Visit 1):

   - If there is more than one assessment of LVEF the value from the most recent measurement should be used in assessing eligibility

   - Patients undergoing coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), valve repair/replacement or implantation of a cardiac resynchronization therapy (CRT) device or any other surgical, device or pharmacological intervention (ie initiation of a beta-blocker) that might improve LVEF must have a measurement of LVEF at least 3 months after the intervention in order to be eligible

   NB: Patients with known HFrEF but without a recent (≤12 months) assessment of left ventricular (LV) function will undergo a local echocardiogram at the time of enrolment.

5. N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥600 pg/ml (or if hospitalised for heart failure within the previous 12 months, NT-proBNP ≥400 pg/ml) at enrolment (visit 1)

   - If concomitant atrial fibrillation or atrial flutter at Visit 1, NT-proBNP must be ≥900 pg/ml (irrespective of history of heart failure hospitalisation)

6. Patients should receive background standard of care for HFrEF and be treated according to locally recognized guidelines with both drugs and devices, as appropriate. Guideline-recommended medications should be used at recommended doses unless contraindicated or not tolerated. Therapy should have been individually optimized and stable for ≥4 weeks (this does not apply to diuretics – see NB below) before visit 1 and include (unless contraindicated or not tolerated):

   - an ACE inhibitor, or ARB or sacubitril/valsartan

   and

   - a beta-blocker

It is essential to collect data for all patients throughout the study. Optimally, a patient who discontinue from IP should for that reason attend all study visits according to plan until study closure. Alternatively, if the patient does not agree to this approach, modified follow-up should be arranged. Patients who agree to some kind of modified follow up are still participating in the study. The modified visits and procedures that are done will be recorded in the electronic Case Report Form (eCRF).

If a patient for some reason cannot be reached during the study, every attempt should be made to retrieve as much information regarding this patient as possible. The site should continuously try to reach the patient, the patient's family or pre-identified contact person and search for information regarding the patient's status in applicable sources to protect the validity of data. The attempts should be registered in the medical records.

3.9.3.1 Patient undergoes the premature treatment discontinuation visit (PTDV) and continues according to plan

The preferred follow-up approach for all patients who prematurely and permanently discontinue IP is that the patient undergoes the premature treatment discontinuation visit (PTDV) and then continues study visits according to plan (see Table 1). The PTDV should be done as soon as possible after last IP dose.

3.9.3.2 Patient agrees to undergo modified follow-up

If the patient does not agree to continue study visits according to plan, but agrees to undergo modified follow up, a PTDV should be done (see Section 4.2.6). The subsequent visits until the study closure will be done as modified follow-up (e.g., less frequent visits, regular telephone contacts, a contact at study closure, or other means) in order to ascertain whether any endpoints or safety events have occurred.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are enrolled patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Screen Failure' (i.e., patient does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment. Withdrawal of consent should only occur if the patient does not agree to any kind of further assessments or contact whatsoever. If agreed by the patient, a PTDV should be performed. Discontinuation of IP in itself is not considered withdrawal of consent.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AZ Biobank during the entire life cycle.

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of donated biological samples is an optional part of the study, the patient may continue in the study.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified as soon as possible to AZ Ensures that biological samples from that patient, if stored at the study site, are identified as soon as possible, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent as soon as possible and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal

AZ ensures the laboratory(ies), or biobank holding the samples is/are informed about the withdrawn consent as soon as possible and that samples are disposed of/destroyed and the action documented and returned to the study site.

5.8 Echocardiographic Sub-study

An echocardiographic sub-study is planned to be conducted in a subset of patients (approx. 300-400 patients) in the Dapa-HF trial. The sub-study is designed to evaluate the impact of dapagliflozin at a dose of 10 mg daily, compared to placebo, in addition to conventional heart failure treatment, on changes in cardiac structure and function as determined by echocardiography.

Enrolment will be restricted to a subset of sites for the main Dapa-HF trial. At participating sites, eligible patients for the main trial, excluding patients with atrial fibrillation at ECG at visit 1, who consent to participation in the sub-study will undergo digitally acquired protocol echocardiograms at randomization and at 8 months post-randomization.

6.3.3 Causality collection

The investigator will assess causal relationship between the IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A.

6.3.4 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF (if fulfilling the criteria as specified in Section 6.3.1). When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.5 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

6.4 Reporting of serious adverse events (SAEs)

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1**

6.7 Management of IP related toxicities (not applicable)

6.8 Study governance and oversight

6.8.1 Executive Committee

Together with AZ, the Executive Committee will be responsible for the final overall study design, including the development of the study protocol and eCRF, supervision of the study conduct and progress, development of any protocol amendments needed during the study, liaison with the CEA, DMC and DKA committee as needed, development of the statistical analysis plan, interpretation of the final data and reporting (presentations at international congresses and publications in peer reviewed journals) of the study.

The Executive Committee will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on the information received from the DMC. The Executive Committee will be comprised of designated international academic leaders and non-voting members of the Sponsor, and will operate under an Executive Committee charter.

6.8.2 National Lead Investigator (NLI) Committee

The National Lead Investigator (NLI) Committee will be comprised of NLIs from each country where the study is conducted and supervised by the Executive Committee. Members of the committee will be responsible for providing clinical guidance on study implementation, recruitment and study conduct in their respective country.

6.8.3 Data Monitoring Committee (DMC)

An independent DMC will be appointed and will report to the Executive Committee. The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the study. The DMC will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing. A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee.

6.8.4 Clinical Event Adjudication (CEA) Committee

The role of the CEA committee is to independently review, interpret and adjudicate potential endpoints that are experienced by the patients. Endpoints will be identified preliminary by the investigators, and also by AZ personnel or in the CEA process as specified in the CEA charter.

The CEA committee members will not have access to individual treatment codes for any patient or clinical efficacy endpoint and safety event. The precise responsibilities and procedures applicable for CEA will be detailed in the CEA charter.

- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If an medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product

Table 3 Investigational Product

Investigational product	Dosage form and strength	Manufacturer
Dapagliflozin 10 mg	Green, plain, diamond shaped, film coated tablets 10 mg	AstraZeneca
Matching placebo for Dapagliflozin 10 mg	Green, plain, diamond shaped, film coated tablets placebo	AstraZeneca
Dapagliflozin 5 mg	Green, plain, diamond shaped, film coated tablets 5 mg	AstraZeneca
Matching placebo for Dapagliflozin 5 mg	Green, plain, diamond shaped, film coated tablets placebo	AstraZeneca

Dapagliflozin and its matching placebo tablets will be packed in bottles. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

7.2 Dose and treatment regimens

At randomisation, Visit 2 (day 0), eligible patients will be randomly assigned to 1 of 2 treatments:

- Dapagliflozin 10 mg, given once daily per oral use
- Placebo – one placebo tablet to match dapagliflozin 10 mg, given once daily per oral use

Randomisation and treatment pack assignment will be managed via an IxRS at Visit 2. The IP should be taken once daily in the morning and at approximately the same time every day, during the study period. If the patient, for any reason prefers not to administer the IP in the

subgroups separately. The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. Treatment differences with 95% confidence intervals will be reported for each subgroup. HRs and CIs for overall analysis and subgroups will be presented with forest plots as well. Further details of the subgroup analysis, including the list of subgroup variables, will be provided in the SAP.

8.5.6 Interim analysis

An interim analysis is planned to be performed when 75% of the primary events are adjudicated, using a Haybittle-Peto rule. There will in principle be one planned interim analysis, with the possibility of the DMC to do subsequent interim analysis if they deem necessary. The significance level for final analysis will be determined by the Haybittle-Peto function based on the actual number and timing of interim analyses. The interim analysis will assess superiority of dapagliflozin to placebo. The interim analysis will have a one-sided alpha level of 0.001. At the interim analysis, the primary composite endpoint will be firstly tested at the specified alpha level. If superiority is achieved for the primary endpoint, then the superiority of dapagliflozin to placebo on CV deaths will be tested at a one-sided level of 0.001. If CV death is significant, then an action is triggered whereby the DMC will evaluate the totality of the efficacy data and safety data, to determine if benefit is unequivocal and overwhelming such that the DMC recommends ending the study.

8.5.7 Sensitivity analysis

Details of the sensitivity analysis will be provided in the SAP.

8.5.8 Analysis of safety variables

The number and percent of patients with SAEs, DAEs, AEs leading to dose reductions and temporary interruptions, and AEs of interest, will be summarized by treatment group. Changes in clinical chemistry/haematology parameters will be summarized over time by treatment group. In addition, the number and percent of patients with a marked abnormality in clinical laboratory tests will be summarized over time by treatment group.

For safety analyses, summaries will be provided using both on treatment observations and using all observations regardless of whether patients are on or of study treatment.

8.5.9 Exploratory analysis

The exploratory variables (excluding PK and biomarkers for future exploratory research) will be analysed as specified in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the site personnel and also

If there are any substantial changes to the study protocol, then these changes will be implemented in a new version of the protocol.

The new version of the study protocol is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for new version protocols.

AZ will distribute any subsequent new versions of the protocol to each PI. For distribution to IRB/IEC see Section 10.3.

If a new version of the protocol requires a change to a site's ICF, AstraZeneca and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an IRB/IEC may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the study site.

11. LIST OF REFERENCES

Ambrosy et al 2014
Ambrosy AP, Gheorghiade M, Chioncel O, Mentz R J, Butler J. Global perspectives in hospitalised heart failure: regional and ethnic variation in patient characteristics, management and outcomes. J Am Coll Cardiol 2014; 63:1123-33.

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Bays HE, Weinstein R, Law G, Canovatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. Obesity (Silver Spring) 2014 Apr; 22(4):1042-9.

Braunwald 2015
Braunwald E. The war against heart failure: the Lancet lecture. Lancet 2015; 385:812-24.

Cook et al 2014
Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol 2014; 171:368-378.

E3 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

The following questions refer to your heart failure and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of heart failure have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐