Supplementary Online Content

Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA*. Published online March 27, 2020. doi:10.1001/jama.2020.1906

Original trial protocol

Final protocol

Summary of changes

This supplementary material has been provided by the authors to give readers additional information about their work.

AstraZeneca

Clinical Study Protocol

Drug Substance	Dapagliflozin
Study Code	D1699C00001
Version	1.0
Date	26 October 2016

Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction

Sponsor: AstraZeneca AB, [redacted]

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

VERSION HISTORY

Version 1.0, 26 October 2016
Initial creation

PROTOCOL SYNOPSIS

Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction

International Co-ordinating Investigator

[redacted]

Study site(s) and number of patients planned

It is estimated that approximately 7000 patients at 500-600 sites in 20-25 countries will be enrolled to reach the target of approximately 4500 randomized patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2017	Phase III
Estimated date of last patient completed	Q4 2019	

Study design

This is an international, multicentre, parallel group, event-driven, randomized, double-blind, placebo-controlled study in patients with chronic heart failure with reduced ejection fraction (HFrEF), evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background regional standard of care therapy, for the prevention of cardiovascular (CV) death or reduction of heart failure (HF) events.

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 (hospitalization for HF or equivalent HF event, ie an urgent HF visit).	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalization for HF 3. An urgent HF visit

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

Secondary Objective:	Outcome Measure :
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 IP due to Adverse Events (DAEs) 3. Changes in clinical chemistry/haematology parameters 4. Adverse events of interest (volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis, AEs leading to amputation)

Target patient population

The target population includes male and female patients with an established diagnosis of HFrEF for ≥2 months, and at high risk of cardiovascular death or heart failure events.

The study population will include patients with NYHA Class II-IV HF with reduced left ventricular ejection fraction (LVEF≤40%), increased N-terminal pro-B-type natriuretic peptide levels and estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m2. Patients should be clinically stable and optimized on heart failure therapies according to local guidelines at the time of enrolment (and background standard of care therapy for type 2 diabetes when applicable). To ensure stability, doses of evidence based heart failure 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 type 2 diabetes, as the beneficial haemodynamic effects of dapagliflozin appear to be independent of the glycaemic effect, and can therefore be expected in both groups. To ensure balance between the diabetic and non-diabetic cohorts, stratification will be employed, with inclusion of at least 30% of each cohort.

Duration of treatment

This study is event driven. The anticipated duration of the study is approximately 33 months with an estimated mean treatment period for a patient of 24 months. The study closure

procedures will be initiated when the predetermined number of adjudicated primary endpoints are predicted to have occurred (n=844) ie, the study end date (SED). The study duration may be changed if the event rate or randomization 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 Data Monitoring Committee (DMC) review.

Investigational product, dosage and mode of administration

Patients will be randomized 1:1 to either dapagliflozin 10 mg or placebo. Every attempt should be made to maintain patients on dapagliflozin 10 mg or matching placebo during the course of the study. In addition to the preferred 10 mg dose, the 5 mg dose of dapagliflozin can be used in the study when clinically indicated. If the dose has been decreased to 5 mg, the dose should be increased back to dapagliflozin 10 mg or matching placebo as soon as, in the opinion of the investigator, the patient's condition is stable.

Statistical methods

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio of 0.80 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 844 primary endpoint events will provide a statistical power of 90% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo.

The study is event-driven. With an annual event rate of 11% in the placebo treatment group, 4500 patients are estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months.

All patients who have been randomized to study treatment will be included in the Full Analysis Set irrespective of their protocol adherence and continued participation in the study. 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 adjudication.

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 randomization, and adjusting for history of hospitalization for heart failure. The p-value, hazard ratio and 95% confidence interval will be reported.

An interim analysis is planned to be performed when 75% of the primary endpoints are adjudicated, using a Haybittle-Peto rule. The interim analysis will assess superiority of dapagliflozin to placebo.

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilized. No multiplicity control is placed on the exploratory endpoints.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACE-I	Angiotensin converting enzyme inhibitor
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARB	Angiotensin receptor blockers
AST	Aspartate transaminase
AZ	AstraZeneca, sponsor
BP	Blood pressure
CHF	Congestive Heart Failure
CABG	Coronary Artery Bypass Grafting
CDISC	Clinical data interchange standards consortium
CEA	Clinical Event Adjudication
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CRO	Clinical research organisation
CRT	Cardiac resynchronization therapy
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
DAE	Adverse event leading to discontinuation of investigational product
DKA	Diabetic ketoacidosis
DMC	Data monitoring committee
DMP	Data management plan
EASD	European Association for the Study of Diabetes
E-code	Enrolment code
eCRF	Electronic Case Report Form

Abbreviation or special term	Explanation
ePRO	Electronic patient reported outcomes
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
EQ-5D-5L	EuroQol five-dimensional five-level questionnaire
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HbA1c	Glycosylated haemoglobin
hCG	Human Chorionic Gonadotropin
HCP	Health care professional
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
IB	Investigator´s brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product (dapagliflozin or matching placebo)
IRB/IEC	Institutional review board/ Independent ethics committee
ITT	Intention to treat
IxRS	Interactive Voice/Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LSLV	Last Subject Last Visit
LIMS	Laboratory information management system
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MRA	Mineralcorticoid receptor antagonist

Abbreviation or special term	Explanation
MRI	Magnetic Resonance Imaging
NSAID	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetic
PRO	Patient reported outcomes
PTDV	Premature treatment discontinuation visit
RAAS	Renin-angiotensin-aldosterone system
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCV	Study closure visit
SED	Study end date
SGLT2	Sodium glucose co-transporter 2
SU	sulfonylurea
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes
TIA	Transient ischemic attack
ULN	Upper limit of normal
VAD	Ventricular assistance device
VAS	Visual analogue scale
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Despite advances in management and treatment of chronic heart failure (HF) with reduced ejection fraction (HFrEF), HF continues to be a major cause of mortality, initial and recurrent hospitalizations, and suboptimal quality of life. The prevalence and incidence of HF continues to increase globally. An estimated 38 million people are affected by HF worldwide (Braunwald 2015) with over 1 million hospitalizations annually in the United States and Europe (Ambrosy et al 2014). The annual global economic burden in 2012 was estimated to be $108 billion (Cook et al 2014) and is projected to increase dramatically as the population ages.

The current treatment paradigm for HF involves the simultaneous targeting of multiple pathways including the renin-angiotensin-aldosterone axis (RAA), the autonomic system, and symptomatic treatment with diuretics.

Although increased efficacy in the sacubitril/valsartan arm led to early closure of the PARADIGM-HF trial, the mortality rate remained high (McMurray et al 2014, Sacks et al 2014). Even with best possible treatment, the five year survival rate for HF is worse than for most cancers (Braunwald 2015). For patients with chronic HF, worsening symptoms require prompt medical attention, add to the burden of hospital and non-hospital settings and also have a considerable economic impact (Ponikowski et al 2016, Okumura et al 2016).

Recently, in patients with type 2 diabetes (T2D) and high cardiovascular (CV) risk, the sodium glucose co-transporter 2 (SGLT2) inhibitor, empagliflozin (JARDIANCE™), demonstrated a marked reduction in CV mortality (38% relative risk reduction [RRR]), all-cause mortality (32% RRR) as well as 35% RRR in hospitalization from HF compared with placebo when added to background standard of care treatment (Zinman et al 2015). In a secondary analysis of HF outcomes, empagliflozin reduced the risk of hospitalization for HF or cardiovascular death by 28 % in patients with HF at baseline (Fitchett et al 2016).

Dapagliflozin (Forxiga™/Farxiga™) is a highly selective and reversible inhibitor of human renal SGLT2, the major transporter responsible for glucose reabsorption in the kidney. Dapagliflozin's mechanism of action results in a direct and insulin-independent elimination of glucose by the kidneys. In addition to the improved glycaemic control, the persistent loss of glucose with associated calories in the urine, results in a consistent and maintained reduction of the total body weight. Further, dapagliflozin induces a diuresis, natriuresis and a decrease in blood pressure without a concomitant increase in heart rate.

Possible mechanisms for SGLT2 inhibitor benefit in patients with heart failure could include osmotic diuresis and reductions in arterial stiffness, weight, blood pressure, serum uric acid and albuminuria. Other potential mediators include a shift in fat oxidation and increased circulating concentrations of ketone bodies which may serve as a more efficient fuel source

for the failing heart (Ferrannini et al 2016). The alterations in haemodynamics and renal physiology are attributed to glucose-independent mechanisms and can therefore be expected to be similar even in the absence of diabetes (Rajasekeran et al 2016).

Data on the effect of SGLT2 inhibition in patients without diabetes is limited. However, dapagliflozin has safely been administered in healthy volunteers over a broad dose range (up to 500 mg given as single dose) (Kasichayanula et al 2014). Dapagliflozin effectively inhibited SGLT2 also in healthy volunteers without any observed events of hypoglycaemia. Furthermore, a clinical study with canagliflozin (INVOKANA™), showed clinically relevant blood pressure and weight reductions in obese non-diabetic patients without an increased incidence of hypoglycaemia (Bays et al 2013).

Dapagliflozin has been investigated in a thorough T2D clinical development program. In addition, the trial DECLARE-TIMI58 (D1693C00001) is ongoing and includes >17,000 T2D patients with elevated CV risk to evaluate dapagliflozin 10 mg on CV outcome.

Available data from a CV outcome meta-analysis showed that dapagliflozin is not associated with increased CV risk and the results even suggested the potential for a beneficial effect on heart failure hospitalizations (Soneson et al 2016). In a post-hoc analysis from the pooled database from the dapagliflozin development program, patients with a history of T2D and concomitant heart failure (171 patients received dapagliflozin 10 mg and 149 patients received placebo), had a significant reduction in weight, blood pressure and HbA1c and dapagliflozin was well tolerated. Volume depletion and hypoglycaemia adverse events (AEs) were balanced between the groups (Kosiborod et al 2015). Although very few HF hospitalization events occurred, numerically these favoured dapagliflozin vs placebo.

The aim of the proposed study is to investigate the efficacy and safety of dapagliflozin in patients with an established diagnosis of HFrEF (with or without T2D) where the prevalence and unmet needs for reducing CV mortality and heart failure events as well as improving symptoms remain high.

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for study design and population

This is a randomized, double-blind, parallel-group study. Randomization and double blinding will minimize potential bias. This will be a multicentre study in numerous geographic regions to provide a wide applicability of results.

The target population includes male and female patients with an established diagnosis of HFrEF for ≥2 months, and at high risk of CV death or HF events.

Although patients may have been previously hospitalised for HF (but prior hospitalisation is not required) they must be clinically stable and optimized on HF therapies according to local 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, ie 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 hospitalization for HF or equivalent event (ie an urgent HF visit) when added to background standard of care treatment. A HF event is defined as hospitalization for worsening HF or an equivalent event (ie an urgent HF visit leading to an urgent, unplanned, assessment by a physician (eg 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 hospitalization in HF treatment, the more inclusive definition of "a heart failure event" is used. HF events consisting of both HF hospitalizations 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 hospitalization, using the more traditional measure of HF hospitalization only, risks missing a significant number of events.

The CDISC definitions of urgent HF visit are similar to those for heart failure hospitalization (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 hospitalization for HF, but excluding non-hospitalized 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 hospitalizations (including re-hospitalizations) for HF is to capture the impact of recurrent non-fatal HF hospitalizations. 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 hospitalizations 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 EP 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 pharmacodynamic 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 (eGFR 30 to 60 mL/min/1.73m2) (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 pharmacodynamic 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, 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 ACE inhibitor (ACE-I) or 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.

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 dapaglifozin or placebo will be administered on top of this treatment. The hypothesis is that dapagliflozin will reduce CV mortality or hospitalization 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 hospitalization 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 hospitalization 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.

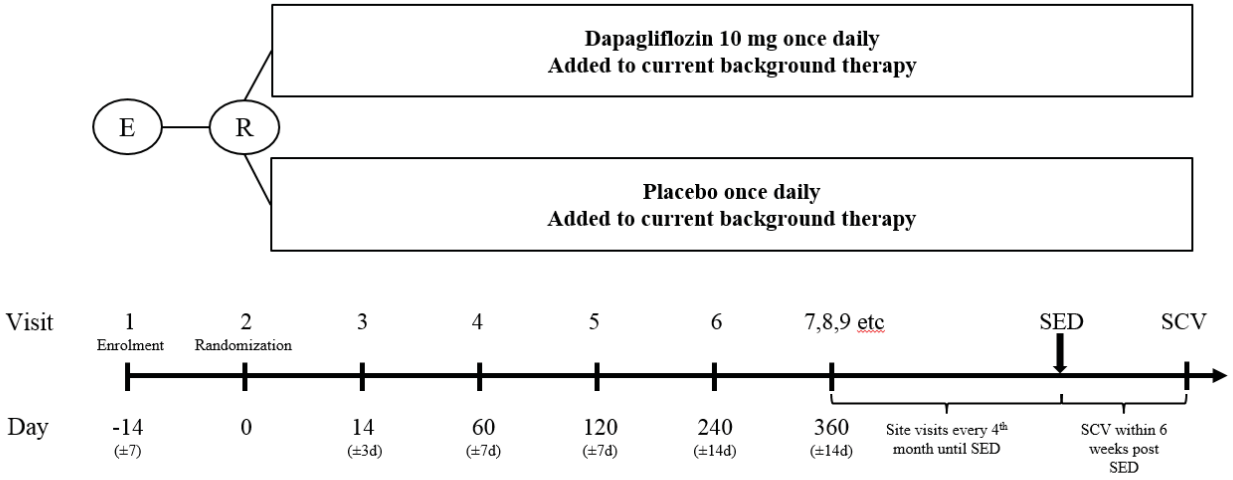
1.4 Study Design

This is an international, multicentre, parallel group, event-driven, randomized, double-blind, placebo-controlled study in patients with chronic HFrEF, evaluating the effect of dapagliflozin 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 randomized 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 adjudicated primary endpoints is predicted to have occurred (n=844), ie, the study end date (SED) (see Figure 1). The study duration may be changed if the event rate or randomization 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.

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

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 (hospitalization for HF or equivalent HF event, ie an urgent HF visit)**.**	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalization 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 hospitalization for HF.	Time to the first occurrence of either of the components of this composite: 1. CV death 2. Hospitalization for HF
To compare the effect of dapagliflozin versus placebo on total number of recurrent HF hospitalizations and CV death.	Total number of (first and recurrent) HF hospitalizations and CV death.
To compare the effect of treatment with dapagliflozin versus placebo on the KCCQ clinical summary score for HF symptoms and physical limitations.	Change from baseline measured at 8 months in the overall summary score of the KCCQ, a specific HF patient reported outcome questionnaire.

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. Adverse events of interest (volume depletion, renal events, major hypoglycaemic events, fractures, Diabetic ketoacidosis (DKA), AEs leading to amputation)

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. Hospitalization 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 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, hemorrhagic, 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 collect and store samples of plasma and serum for future exploratory biomarker research.	Not applicable. Results will be reported separately.

3. PATIENT SELECTION, ENROLMENT, RANDOMIZATION, 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

3. Established documented diagnosis of symptomatic HFrEF (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. 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 device (CRT) or any other surgical, device or pharmacological intervention (eg 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 LV function will undergo a local echocardiogram at the time of enrolment.

5. NT-proBNP ≥600 pg/ml (or if hospitalized for heart failure within the previous 12 months, NT-proBNP ≥400 pg/ml) at enrolment (visit 1)

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

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

   and

   – if considered appropriate by the patient's treating physician; a mineralcorticoid receptor antagonist (MRA)

   NB: Most patients with heart failure require treatment with a diuretic to control sodium and water retention leading to volume overload. It is recognized that diuretic dosing may be titrated to symptoms, signs, weight and other information

and may thus vary. Each patient should, however, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual.

7. eGFR ≥30 ml/min/1.73 m^2 (CKD-EPI formula) at enrolment (visit 1)

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor

2. Type 1 diabetes mellitus (T1D)

3. Symptomatic hypotension or systolic BP <95 mmHg on 2 consecutive measurements

4. Current acute decompensated HF or hospitalization due to decompensated HF <4 weeks prior to enrolment

5. MI, unstable angina, stroke or transient ischemic attack (TIA) within 12 weeks prior to enrolment

6. Coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo any of these operations after randomization

7. Implantation of a cardiac CRT within 12 weeks prior to enrolment or intent to implant a CRT device

8. Previous cardiac transplantation or implantation of a ventricular assistance device (VAD) or similar device, or implantation expected after randomization

9. HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy or uncorrected primary valvular disease

10. Symptomatic bradycardia or second or third degree heart block without a pacemaker

11. Any condition outside the CV and renal disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator´s clinical judgement

12. Active malignancy requiring treatment at the time of visit 1(with the exception of successfully treated basal cell or treated squamous cell carcinoma)

13. Hepatic impairment aspartate transaminase [AST] or alanine transaminase [ALT] >3x the upper limit of normal [ULN]; or total bilirubin >2x ULN at time of enrolment)

14. Known blood-borne diseases such as specified in Appendix B (category A and B)

15. Severe (eGFR <30 mL/min/1.73 m2 by CKD-EPI), unstable or rapidly progressing renal disease at the time of randomization

16. Women of child-bearing potential (ie, those who are not chemically or surgically sterilised or who are not post-menopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator OR women who have a positive pregnancy test at enrolment or randomization OR women who are breast-feeding

17. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site)

18. Previous randomization in the present study

19. Participation in another clinical study with an IP during the last month prior to enrolment

20. Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up OR any conditions that, in the opinion of the investigator, may render the patient unable to complete the study

NB: Patients who cannot complete the ePRO assessments can still participate in the study (see Section 5.1.11.5 for details regarding the patient exclusion from the ePRO assessments during certain circumstances)

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomization

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the patient or their guardian/legal representative before any study specific procedures are performed.

2. Assign patient a unique enrolment number, beginning with ‘E#’, which will be used to identify the patient throughout the study. The enrolment code (E-code) will be assigned in the Interactive Voice/Web Response System (IxRS).

3. Determine patient eligibility, see Section 3.

4. At visit 2, perform the randomization transaction in the IxRS system.

Re-enrolment one single time is allowed considering that the patient has not been previously randomized. The same E-code that the patient received at the first enrolment will be used. All enrolment assessments and procedures, including re-signing the informed consent form, should be performed again.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. Regardless of what is decided about IP, all randomized patients should remain in the study. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Randomization to IP will be performed via IxRS at Visit 2 in balanced blocks to ensure approximate balance between the treatment groups (1:1).

The IxRS will allocate the IP through a randomization scheme and provide the randomization number and the appropriate Kit IDs from IP available at the study site. The randomization codes will be computer generated and loaded into the IxRS database.

At all visits where IP is dispensed, site personnel will do a kit verification in IxRS before providing the IP bottle to the patient. Detailed instruction on how to use the IxRS system will be provided to study sites.

3.5.1 Stratification and capping

The recruitment will be continuously monitored in order to achieve adequate proportions of patient sub-populations.

3.5.1.1 Stratification

Randomization will be stratified in IxRS based on patients with and without T2D at the time of randomization in order to ensure approximate balance between treatment groups within each sub-population. T2D at the time of randomization is based on:

- Established diagnosis of T2D

OR

- HbA1c more or equal to 6.5% (48 mmol/mol) shown at central laboratory test at enrolment (visit 1)

3.5.1.2 Capping

The intent is to enrol as typical cross-section of patients with HFrEF and to include representative proportions of diabetic and non-diabetic patients. The number of randomized patients with and without T2D will be monitored in order to ensure a minimum of 30% in each sub-population. Randomization may be capped (ie, no more patients can be randomized in a specific sub-population) if the pre-determined limit is reached.

Randomization of patients based on geographic region will be monitored to ensure global representation. LVEF value, NYHA class and atrial fibrillation status may be capped in IxRS to avoid over- or under-representation of these patient subgroups.

3.6 Methods for ensuring blinding

The blinding of treatment is ensured by using a double-blind technique. The dapagliflozin tablets and the respective placebo tablets will be identical in size, colour, smell, and taste. The bottles with IP will be labelled with unique identification numbers.

No member of the extended AZ study team, personnel at study sites, or any CRO handling study data will have access to the randomization scheme during the study. The AZ personnel or delegate generating the randomization scheme and the Supply Chain Study Management may be able to access the randomisation scheme as appropriate.

3.7 Methods for unblinding

Individual treatment codes, indicating the randomised treatment for each patient, will be available to the investigator(s) or pharmacists from the IxRS. Instructions for code breaking/ unblinding will be described in the IxRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca personnel. It is always the investigator who decides when to unblind but it is recommended that the investigator first contacts the AZ study physician for consultation regarding the need for unblinding. If unblinding is deemed necessary, the investigator can perform the unblinding in IxRS and must document all actions taken. The number of individuals at the study site who become aware of treatment status should be kept to the absolute minimum (including keeping the patient blinded if possible). Treatment with study medication should be continued if possible.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.7.1 Unblinding for bioanalytical laboratory personnel

PK samples will be analysed at the bioanalytical laboratory only for patients on active IP. The bioanalytical laboratory will therefore have access to the treatment codes but will not share the codes with the sponsor or others involved in the study until the blinding is broken for the study after closure.

3.8 Restrictions

There are no specific dietary or activity restrictions. For restricted concomitant medications see Section 7.7.

3.9 Discontinuation of investigational product

If the patient temporarily or permanently discontinues from IP, it is important that the scheduled study visits, data collection and procedures continue according to the study protocol until study closure (see Section 3.9.3).

Patients may be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.

2. AE or other safety reasons that, in the opinion of the investigator, contraindicates further dosing with IP

3. Severe non-compliance with the study protocol

4. DKA, consider to temporary interrupt IP if DKA is suspected. If DKA is confirmed, IP should be discontinued permanently.

5. Positive pregnancy test (discontinue IP and notify AZ representative)

3.9.1 Evaluation of volume status and investigational product (IP) dose reduction/interruption

Dapagliflozin is a SGLT2 inhibitor which by its mechanism of action reduces the reabsorption of glucose and sodium in the proximal tubules in the kidney. SGLT2 inhibition has a mild diuretic effect and an initial haemodynamic change with an initial increase in creatinine may occur.

Unexpected acute declines in eGFR

If an unexpected, acute decline in kidney function is observed, the patient should be evaluated. Volume depletion, hypotension, inter-current medical problems and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered (the latter especially in men). Several drugs may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs (NSAID) and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be re-considered.

Volume depletion/hypotension

Patients with clinically relevant symptoms/signs of suspected volume depletion and/or hypotension, should have their regular medication reviewed, and consideration given to reducing the dose of, or stopping concomitant non-essential medications, as assessed on an individual basis, including diuretics and drugs that lower blood pressure (except essential treatments – see below). The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in light of the patient's symptoms and signs. In patients with heart failure, discontinuation of diuretic should only be undertaken cautiously. Hypotension may also occur with other blood pressure lowering drugs and once again the need for (and dose of) non-essential agents of this type (eg, calcium channel blockers, alpha adrenoceptor antagonists and nitrates) should also be re-considered.

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.

IP dose reduction

If the above mentioned measures do not lead to a resolution of clinically relevant volume depletion, hypotension and/or unexpected worsening of kidney function, a dose reduction of IP to dapagliflozin 5 mg or matching placebo may be considered and the patient's condition re-evaluated.

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 (eg 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 randomized IP is always encouraged. Whenever possible, randomized IP should be restarted if stopped or the dose increased if previously reduced. Even if a PTDV was

completed due to discontinuation of IP, this should not prevent the patient to return to randomized 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.

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 (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 (eg, 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 randomized. These patients should have the reason for study withdrawal recorded as 'Screen Failure' (ie, patient does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures (not randomized 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.

Withdrawal of consent must be ascertained and documented in writing by the investigator who must inform the AZ representative and document the withdrawal of consent in the eCRF and medical records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs reported outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment and randomization codes cannot be reused. Withdrawn patients will not be replaced. Data generated to the time of complete withdrawal from the study will not be destroyed.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at study closure (also for patients who have withdrawn their informed consent). The investigator will therefore attempt to collect information on all patients' vital status from publicly available sources at study closure, even if informed consent has been withdrawn completely, in compliance with local privacy laws/practices.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, patients are placed at undue risk because of clinically relevant findings. The judgment may be based on recommendations from the DMC, see DMC Charter for details. The study can also be stopped based on results of the interim analysis (see Section 8.5.6)

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

The schedule of study visits and assessments is shown in Table 1 and explained further in Sections 4.1 and 4.2.

Table 1 Study plan

Activity	**Enrolment**	**Randomi-zation**	**Site visits**					**PTDV**	**SCV**	**Reference CSP**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9 etc.**	**PTDV**	**SCV**	
Day	**-14** (±7)	**0**	**14** (±3)	**60** (±7)	**120** (±7)	**240** (±14)	**Day 360** (±14 and every 4th month)		**≤6 wks from SED**	
Sign Informed Consent Form (ICF)	X									
Local laboratory assessment of NT-proBNP[a]	X[a]									
Inclusion/exclusion criteria	X	X								3.1
Demography	X									
Medical/surgical history	X									
General physical examination	X							X	X	5.2.1.2
Targeted physical examination		X	X	X	X	X	X			5.2.1.2
Assessment of left ventricular function[b]	X									4.1.1
NYHA Functional Classification	X				X	X		X	X	5.1.6
Electrocardiogram (ECG)	X									5.2.2
Height	X									5.2.3.2
Vital signs *(BP, pulse and body weight)*	X	X	X	X	X	X	X	X	X	5.2.3
Pregnancy testing	X	X								4.1.1
Randomization in IxRS		X								3.5

Activity	**Enrolment**	**Randomi-zation**	**Site visits**					**PTDV**	**SCV**	**Reference CSP**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9 etc.**	**PTDV**	**SCV**	
Day	**-14** (±7)	**0**	**14** (±3)	**60** (±7)	**120** (±7)	**240** (±14)	**Day 360** (±14 and every 4th month)		**≤6 wks from SED**	
Concomitant medication		X	X	X	X	X	X	X	X	7.7
Central laboratory assessments[c]	X	X	X	X	X	X	X	X	X	5.2.1
PK sampling (predose)[d]							X			5.4
ePRO questionnaires[e]		X			X	X	X[d]	X	X	5.1.9
Potential endpoint events, SAEs, DAEs, AEs of interest[f]	X	X	X	X	X	X	X	X	X	5.1.1
Dispense IP (including kit verification in IxRS)/Collect IP		X			X	X	X	X	X	7.2
IP compliance reminder		X	X	X	X	X	X			7.5
Sample for future biomarker research, optional[g]		X					X			5.7

[a] Local laboratory assessment is optional and may be used to assess eligibility (according to local routine) of NT-proBNP. If used, the ICF need to be signed before the optional assessment starts. The optional local laboratory assessment can be done up to 3 months prior to randomization.

[b] LV assessments only if no assessment has been performed within 12 months prior to enrolment.

[c] Central laboratory assessments include alkaline phosphatase (ALP), ALT, AST, bilirubin, blood urea nitrogen (BUN), creatinine (including eGFR assessment), haematocrit, haemoglobin (Hb), HbA1c, NT-proBNP, phosphate, potassium, and sodium, as specified in Table 2.

[d] PK samples will be collected at visit 7.

[e] PGIS, KCCQ, EQ-5D-5L will be filled in at visit 2,5,6,7 and every 12 months after visit 7, and at PTDV and SCV. PGIC will be filled in at the same visits, with exception of visit 2.

[f] SAEs will be collected from the time of informed consent throughout the study until and including the patient's last visit. Potential endpoints, DAEs, AEs leading to dose reduction and temporary interruptions and AEs of interest will be collected from randomization throughout the study until and including the patient's last visit.

[g] Blood samples for potential future biomarker research will be collected at visit 2 and visit 7 and may be analysed at the discretion of AstraZeneca. The biomarker sampling is subject to separate approval/consent by the patient and is optional.

4.1 Enrolment period

4.1.1 Visit 1, Enrolment (Day -14±7)

At enrolment the following assessments and procedures will be completed:

- Patient signs the **ICF**
  - Patients who agree to the optional sampling of blood for potential future biomarker research will provide their consent. The biomarker consent is optional and included in the main ICF.
- The patient will be **enrolled** and assigned an **E-code in IxRS**.
- **Optional local laboratory assessment**

  Failure to meet the criteria for NT-proBNP is expected to be the main reason for screen failure in this study. Therefore, sites will be allowed to perform an optional pre-study assessment, which will comprise of local assessment of NT-proBNP. Investigators will only assess patients who are potentially eligible for the study based on their medical conditions and existing therapies, and only those who are expected to meet all other entry criteria.

  Local laboratory assessment of NT-proBNP will be done according to local routine.

Based on the clinical judgement of the investigator, the patient may proceed to further enrolment procedures:

- The investigator reviews the **inclusion and exclusion criteria**. Patients who do not meet these criteria must not be enrolled in the study.
- **Demography** (date of birth, sex, race, ethnic group) and **relevant medical and surgical history,** including smoking history, will be recorded.
- The investigator will perform a **general physical examination** (see Section 5.2.1.2).
- Assessment of **left ventricular function** will be performed if no assessment has been performed within 12 months prior to enrolment (echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI).
- **NYHA** Functional Classification will be evaluated.
- **ECG** will be recorded.

- **Vital signs** (BP, pulse and body weight) and **height** will be assessed and recorded.
- **Laboratory samples** will be collected and sent to central laboratory as specified in Table 2.
- **Pregnancy test** for women of child-bearing potential will be done locally with a dipstick provided by central laboratory.

4.2 Treatment period

4.2.1 Visit 2, Randomization (Day 0)

Prior to visit 2, the investigator will review laboratory results received from the central laboratory and assess eligibility based on the laboratory results from visit 1. Patients not eligible will be considered screen failures and should not continue to visit 2.

At randomization, the following assessments and procedures will be done:

- **PGIS, KCCQ** and **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will re-assess the **inclusion** and **exclusion criteria**
- **Randomization** to IP will be done in IxRS
  - For stratification/capping purposes, the information whether patient has T2D or AF, LVEF value and NYHA class will be recorded in IxRS (see Section 3.5.1).
- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.
- **Vital signs** will be assessed and recorded.
- **Concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
  - Patients who have consented to sampling for potential future **biomarker analysis**, will provide blood samples for this purpose.
- **Pregnancy test** for women of child-bearing potential will be done locally with a dipstick provided by central laboratory.
- If the patient has experienced any **SAEs** since last visit, this will be recorded in the eCRF.

- **IP** will be dispensed via IxRS to the patient. The patient will be instructed to take the IP in accordance with protocol without interruptions and, to bring all dispensed bottles to all study visits.

4.2.2 Visit 3 (Day 14±3) and Visit 4 (Day 60±7)

At visit 3 and visit 4, the following assessments and procedures will be done:

- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medication** will be recorded, see Section 7.7.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- The patient will continue taking the study medication dispensed at the last visit. IP compliance will be discussed. The patient will be reminded to take the IP in accordance with protocol and without interruptions.

4.2.3 Visit 5 (Day 120±7)

At visit 5, the following assessments and procedures will be done:

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.
- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medication** will be recorded.
- L**aboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.

- New **IP** will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be reminded to take the IP in accordance with protocol and without interruptions.

4.2.4 Visit 6 (Day 240±7)

At visit 6, the following assessments and procedures will be done:

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the Investigator.
- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.
- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- New **IP** will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be reminded to take the IP in accordance with protocol and without interruptions.
- Remind the patient that at visit 7 there will be pre-dose PK sampling. The day of visit 7 the patient must delay the intake of study medication until after the visit.

4.2.5 Visit 7, 8, 9 etc (Day 360±14; and every 4th month ±14 days)

At visit 7 and all subsequent on-site visits until SCV, the following assessments and procedures will be done:

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator, at visit 7 and every 12 months thereafter, ie visit 10, 13 etc.
- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.
- **Vital signs** will be assessed and recorded.

- Any changes in relevant **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
  - At visit 7, pre-dose, a **PK sample** will be collected. This day the patient must delay the intake of IP until after the visit. The date and time of last dose before sampling will be recorded in eCRF.
  - At visit 7, patients who have consented to sampling for potential future **biomarker analysis**, will provide blood samples for this purpose.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- **IP** will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be instructed to take the IP in accordance with protocol without interruptions.

4.2.6 Premature Treatment Discontinuation Visit (PTDV)

Patients who prematurely and permanently discontinue treatment with study medication should return for a PTDV, which will be done as soon as possible after last IP dose.

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **general physical examination.**
- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- **Drug accountability** of the returned medication will be checked.

Patients who discontinue treatment prematurely should attend all study visits according to plan, including the Study Closure Visit (SCV). For further details regarding discontinuations from IP, please see Section 3.9.

4.2.7 Study Closure Visit (SCV)

All patients will be asked to return for a SCV when the predetermined number of adjudicated primary endpoint events is anticipated, ie SED. All randomized patients (including any patients who have discontinued treatment with IP) should return for their SCV as soon as possible but no later than 6 weeks after the SED.

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **general physical examination.**
- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medication** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- The patient will return remaining IP and **drug accountability** will be checked.

4.2.8 Unscheduled visits

An unscheduled visit may occur in-between scheduled visits eg, to follow up on potential endpoint events such as re-sampling for eGFR (see Section 5.1.4)

4.3 Follow-up period (Not applicable)

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs in Rave as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA).

The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Endpoint reporting overview

Potential endpoint events will be identified using laboratory data (refer to Table 2 for laboratory assessments and timings), when questioning the patient about his/her overall health, or through information received through standard medical practice. Investigators will be encouraged to have a low threshold to submit any potential/possible event that might represent an endpoint.

The following potential endpoints will be reported and source documents submitted for central adjudication:

- All deaths
- All HF events (hospitalizations for HF or urgent HF visits)
- Potential renal endpoints:
  - eGFR declines ≥50% from baseline
  - eGFR values <15 mL/min/1.73m^2
  - 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)

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 events

All potential HF endpoint events (hospitalizations for HF or urgent HF visits) should be recorded as an AE 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 Appendix C 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

Dialysis, renal transplantation, eGFR events (<15 mL/min/1.73m2, ≥50% decline in eGFR) and doubling of serum creatinine (compared with the most recent central laboratory measurement) will be recorded in the eCRF and submitted for adjudication.

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

Potential renal endpoints related to laboratory values for eGFR and doubling of serum creatinine should be recorded in the eCRF if:

- **Local laboratory** values indicate that eGFR value has declined ≥50% compared with baseline, or is below 15 mL/min/1.73m^2, or if the serum creatinine is doubled.

  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, or if the serum creatinine is doubled.

The central laboratory will notify site if eGFR is <15 mL/min/1.73m^2 or if there is ≥50% decline in eGFR, or in the occasion of doubling of serum creatinine, and request a re-sampling after 4 weeks, and preferably no later than 6 weeks after the first sampling. The central laboratory will also notify the site if the serum creatinine value is ≥2 times the value compared with the most recent central laboratory measurement.

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

5.1.5 Initiation of new, or increased dose of existing oral treatment for worsening of 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 (eg increase in dose of diuretic) sustained for at least 4 weeks, will be reported in the eCRF.

5.1.6 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

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 randomization, 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 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 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 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 Clinical Summary Score incorporates the symptom and physical limitations 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

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 (eg, 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 (eg, 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]
Hematocrit[a]	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]
	NTproBNP[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 eg, eGFR values. Follow-up samples related to eGFR should be collected during an unscheduled visit and sent to central laboratory for analysis.

5.2.1.2 Physical examination

A general physical examination will be performed at the time-points specified in Table 1 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, dyspnea, ascites, 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.

5.2.2 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.

5.2.3 Vital signs

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

5.2.3.1 Pulse and blood pressure

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.

5.2.3.2 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

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 AstraZeneca 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.

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 AstraZeneca
- 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

AstraZeneca 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.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all personnel involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an

undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs. The term AE in this document refers only to the categories of events described in Section 6.3.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix A.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from randomization (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:

- **SAE** (as defined in Section 6.2)
- If the AE is the reason for permanent discontinuation from IP (**DAE**)
- If the AE is the reason for **IP interruption** or **dose reduction**
- An **AE of interest**
  - Volume depletion

- Renal events (including renal potential endpoints as defined in Section 5.1.4)
- Major hypoglycaemic events
- Fractures
- Potential DKAs
- AEs leading to amputation

- **AE leading to a potential endpoint**:
  - All deaths
  - All HF events
  - eGFR declines ≥50% from baseline
  - eGFR values <15 mL/min/1.73m^2
  - 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)
  - New diagnosis of T2D
  - New diagnosis of Atrial Fibrillation

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 (eg, dehydration, hypovolemia, or hypotension) will be recorded in the eCRF as AEs.

6.3.2.2 Renal events

All renal events, including potential endpoints 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 AEs leading to amputation

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.

6.3.3 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.

6.3.4 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 hospitalization
- 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.

6.3.5 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.

6.3.6 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.

6.3.7 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, are the reason for discontinuation of treatment with the IP, qualifies as AEs of interest or, potential endpoints.

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 (eg, 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 ie, 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 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 ie, 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 endpoint events

All components of the primary and secondary efficacy endpoints (ie, deaths, HF events and renal events) in the study will not be reported to health authorities**,** to avoid unnecessary unblinding of efficacy endpoints that are also fulfilling the SAE criteria. Clinical data for potential endpoints 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).

Potential endpoints in the study, including the primary efficacy endpoint as well as the secondary and to some extent the exploratory endpoints, will be centrally adjudicated by an independent CEA committee (see Section 5.1.1 and 6.8.4).

If it is determined by the CEA committee that a potential endpoint does not meet the endpoint criteria, but is judged by investigators to fulfil the SAE criteria, the event will be captured as an SAE, according to the timelines specified in Section 6.4 (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 AstraZeneca 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 AstraZeneca 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 AstraZeneca.

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 AstraZeneca representatives within 1day ie, 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 AstraZeneca 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.

6.7 Management of IP related toxicities (not applicable)

6.8 Study governance and oversight

6.8.1 Executive Committee

Together with AstraZeneca, 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.

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.

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

Investigational product	Dosage form and strength	Manufacturer
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 randomization, 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

Randomization 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 morning, any other time point during the day may be applied, provided the patient routinely administer the IP in approximate 24 hours intervals. The IP should not be altered (eg, crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

If the preferred 10 mg dose is reduced to dapagliflozin 5 mg or matching placebo (see Section 3.9.1) or increased back to 10 mg or matching placebo (see Section 3.9.2), this will be done in IxRS and the dose change will be recorded in the eCRF.

Missed doses of dapagliflozin or placebo blinded study medication should not be compensated for (ie, if a dose is missed, the next regularly scheduled dose should be taken and should not be doubled).

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All IP should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of all investigational products should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

The IP provided for this study will be used only as directed in the study protocol. The site personnel will account for all IP dispensed to and returned from the patient.

Patients will be asked to bring all unused study medication and empty packages to the study site at each site visit. The investigator or delegate will enter the amount of returned tablets in the eCRF. Any patient found to be noncompliant would be counselled on the importance of taking their study medication as prescribed.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

The investigator will retain the returned medication until the AZ representative or delegate collects it, along with any medication not dispensed. The AZ representative or delegate is responsible for confirming the investigator or delegate has recorded the quantities of returned and unused tablets at a patient level before medication is destroyed. The AZ representative or delegate will advise on the appropriate method for destruction of unused study medication.

7.7 Concomitant and other treatments

All patients should be treated according to regional standard of care for HF, CV risk factors (eg blood pressure, lipids, antithrombotic treatment) and diabetes. Background medication will not be provided by the Sponsor.

7.7.1 Prohibited medication

Treatment with open label SGLT2 inhibitors eg, dapagliflozin, empagliflozin and canagliflozin, ertuglifluzin, tofogliflozin and luseogliflozin and fix dose combinations containing these drugs are not allowed for the duration of the study.

7.7.2 Recording of concomitant treatment

Recording of all concomitant medications will be made at the randomization (Visit 2) and SCV. Detailed recording of medications related to HF (see Section 7.7.3) and diabetes (see Section 7.7.4) will be made throughout the study. In addition, concomitant medications will be recorded at the time of any SAEs, potential endpoints and AEs of interest (as defined in Section 6.3.2 and 6.4).

7.7.3 Heart failure (HF) medications

To be eligible, the patient should be on background standard of care therapies for HF according to local guidelines. Standard evidence based treatments will include either an ACE inhibitor, ARB or sacubitril/valsartan in combination with a beta-blocker, as well as an MRA where appropriate unless contraindicated or not tolerated. If the patient for any reason is not on background standard of care medications at baseline, the reason for this will be recorded in the eCRF.

Most patients will also require a diuretic, generally a loop diuretic such as furosemide, to control symptoms. Optimization of volume status, and proactive adjustment of diuretic doses may help minimize any deleterious effects on hypovolemia/volume depletion accentuated by the diuretic effects of the IP.

Patients should remain on stable doses of medications which will allow assessment of incremental dapagliflozin effect. Dose reduction or discontinuation of proven effective therapies should be avoided unless all other measures fail to improve the patient's situation. In heart failure, use of ACE-I/ARBs, Sacubitril/Valsartan, mineralocorticoids and beta-blockers is supported by evidence from previous clinical trials. However, if the patient's condition warrants a change in any of these standard evidence based medications, it will be allowed at the discretion of the investigator. If patients require dose adjustment of background therapy to avoid signs/symptoms of volume depletion, diuretics should be decreased prior to adjusting other medications.

7.7.4 Anti-diabetes treatment

7.7.4.1 Background

More than 40% of patients with established HF are estimated to have T2D (Kristensen et al 2016) and it is expected that a large proportion of patients in this study will have an established diagnosis of T2D when included in this study. Furthermore it is expected that some patients will develop T2D during the course of the study. Treatment of diabetes should follow established guidelines, according to glycaemic goals as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) in their joint Position Statement (Inzucchi et al 2012, Inzucchi et al 2015). In brief, the ADA/EASD recommends lowering HbA1c to < 7.0% in most patients. Less stringent HbA1c goals, eg 7.5 to 8% or even slightly higher may be appropriate for patients with a history of severe hypoglycaemia, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counseling, and effective doses of multiple glucose-lowering agents, including insulin.

7.7.4.2 Treatment of patients with established diagnosis of type 2 diabetes

Patients with T2D at randomization will continue their T2D treatment. Patients are eligible for adjustments in their anti-diabetes treatment at the discretion of their diabetes health care provider. Diabetes medications at baseline and any changes throughout the study, will be recorded in the eCRF.

7.7.4.3 Use of medications known to cause hypoglycaemia in type 2 diabetes

Insulin and insulin secretagogues are known to cause hypoglycaemia. Therefore, patients treated with insulin or SU have a higher risk of experiencing hypoglycaemic events compared with those treated with other antidiabetic agents. Therefore a lower dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia when used in combination with study medication.

Reduction of insulin by 10-20% (total daily dose) and SU by 25- 50% and increased frequency of blood glucose monitoring may be considered in patients receiving insulin and/or SU and with baseline HbA1c <7% at randomization.

7.7.5 Other concomitant treatment

Medications other than described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF as applicable.

7.8 Post Study Access to Study Treatment

Post-study treatment will not be provided by the Sponsor.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violations have been identified and documented.

A comprehensive Statistical Analysis Plan (SAP) will be developed prior to first patient randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

The results of the key study outcome will be independently validated by an external statistical team.

8.2 Sample size estimate

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio (HR) of 0.80 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 844 primary endpoint events will provide a statistical power of 90% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The study is event-driven. The assumed HR of 0.80 is considered as clinically relevant and has taken into account the HF outcomes in the EMPA-REG trial.

With an annual event rate of 11% in the placebo treatment group, 4500 patients are estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months. The assumed placebo event rate of 11% is based on a review of recently published clinical studies in the HFrEF population, including the PARADIGM-HF trial. This study is a group sequential design study with one interim analysis using Haybittle-Peto boundary (a one-sided alpha=0.001), leaving a one-sided alpha of 2.496% for the final analysis. In addition, the expected number of patients who will be lost to follow-up is expected to be small; hence, these are not considered in the determination of the sample size.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

All patients who have been randomized to study treatment will be included in the Full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomized IP assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

8.3.2 Safety analysis set

All patients who received at least 1 dose of randomized 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 randomization, and adjusting for history of hospitalization 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 randomization 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 hospitalization 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 hospitalizations (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 Clinical Summary 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 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. 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, then the superiority of dapagliflozin to placebo on CV deaths will be tested at a one-sided level of 0.001, 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

Sensitivity analysis for the primary composite endpoint with respect to unknown status will be conducted. Further 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 train them in any study specific procedures and the WBDC, ePROs system and other relevant systems utilised.

The PI will ensure that appropriate training relevant to the study is given to all site personnel, and that any new information relevant to the performance of this study is forwarded to the personnel involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other personnel).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s) and site personnel
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, medical records)
- Perform source data review, ie review of source documentation to check quality of source, review protocol compliance, ensure critical processes and source documentation are adequate.
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other personnel at the centre needs information and advice about the study conduct.

9.2.1 Risk based quality management

Quality by design will be implemented, including a focus on identifying key risks to patient safety, data quality, and Good Clinical Practice (GCP)/regulatory compliance, to build quality into the design, conduct, analysis and reporting of the study.

A risk based monitoring approach will be applied for this study. A mix of monitoring strategies will be implemented: on-site monitoring, remote monitoring (site level monitoring activities performed at a location other than the study site) and centralized monitoring systems. Monitoring strategies will be tailored to risks, permit timely oversight (through central/remote monitoring and use of technology), and will be focused on critical processes and critical data.

Central monitoring will be used to check that data is consistent and complete, identify unusual distribution of data, identify higher risk sites to target additional monitoring, and to ensure routine review of data is completed in real time.

9.2.2 Source data

The Clinical Study Agreement (CSA) will specify the location of source data. The investigator must provide direct access to source data/documents for monitoring, audits, Institutional Review Board/Independent Ethics Committee (IRB/IEC) review, and regulatory inspections.

9.2.3 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.4 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last patient undergoing the study’.

The study is expected to start in Q1 2017 and to end by Q4 2019.

The study may be terminated at individual study sites if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre personnel at Cognizant, according to the Data Management Plan (DMP).

Data entered into the eCRF will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be reviewed, queried and updated as needed.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug-Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

The data will be validated as defined in the DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation will be done between the study database and safety database.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Institutional review board/ Independent ethics committee (IRB/IEC) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site personnel.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The IRB/IEC should approve all advertising used to recruit patients for the study.

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.

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

AstraZeneca 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.

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 hospitalized heart failure: regional and ethnic variation in patient characeteristics, management and outcomes. J Am Coll Cardiol 2014; 63:1123-33.

Bays et al 2013
Bays HE, Weinstein R, Law G, Canovatchel W Obesity (Silver Spring). Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. 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.

Ferrannini et al 2016
Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care. 2016 Jul; 39(7):1108-14

Fitchett et al 2016
Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J doi:10.1093\eurheartj\ehv728 [Epub ahead of print].

Ghosh and Lin 2000
Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. *Biometrics* 2000; 56:554–562.

Green et al 2000
C. Patrick Green, MD, Charles B. Porter, MD, FACC, Dennis R. Bresnahan, MD, FACC, John A. Spertus, MD, MPH, FACC Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: A New Health Status Measure for Heart Failure. JACC, Vol.35 No 5, April 2000:1245-55

Hicks et al 2014
Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE et al, on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for Cardivasculare and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC August 20, 2014.

Inzucchi et al 2012
Inzucchi SE, Bergenstal RM, Buse J.B, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statementof the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia.

Inzucchi et al 2015
Inzucchi Silvio E Bergenstal Richard M, Buse John B, Diamant Michaela, Ferrannini Ele, Nauck Michael, Peters Anne L, Tsapas Apostolos, Wender Richard,and Matthews David R. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149

Kasichayanula et al 2014
Kasichayanula S, Liu X, Lacreta F, Griffen SC, Boulton DW. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. Clin Pharmacokinet. 2014 Jan;53(1):17-27.

Kohan et al 2014
Kohan DE, Fioretto P, Tang W and List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin educes weight and blood pressure but does not improve glycemic control. Kidney International 2014; 85:962–971. Diabetes Care 2015; 38:140–149

Kosiborod et al 2015
Kosiborod M, Gause-NilssonvI, J Xu J, Sonesson C, Johnsson E. Efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus and Concomitant Heart Failure. Poster 1211-P at American Diabetes Association; Boston, MA, June 5–9, 2015.

Kosiborod et al 2016
Kosiborod M, Xu J, Sjostrand M, Sjostrom CD Safety and Efficacy of Dapagliflozin in Combination with Potassium-sparing Agents. Abstr, 1094-P ADA, June 2016, New Orleans

Kristensen et al 2016
Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS et al. Risk related to pre–diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail. 2016;9:e002560.

Levey at al 2009
Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5; 150(9):604-12

Lin et al 2000
Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2000; **62**(4):711–730.

McMurray et al 2014
McMurray JJV, Packer M, Desai ASD, Gong JG, Lefkowitz MP et al for the PARADIGM-HF Investigators and Committees. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Eng J Med 2014; 371:993-1004.

Okumura et al 2016
Circulation133:2254-2262.

Ponikowski et al 2016
Ponikowski P, Voors A, Anker S D, Bueno H, Cleland JGF, Coats AJ S, Falk V, González-Juanatey J R, Harjola V P, Jankowska E A, Jessup M, Linde C, Nihoyannopoulos P, Parissis J T, Pieske B, Riley J P, Rosano G M C, Ruilope L M, Ruschitzka F, Rutten F H, Pe van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal (2016) 37, 2129–2200

Rajasekeran et al 2016
Rajasekeran H, Lytvyn Y and Cherney DZI. Sodium–glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis. Kidney International 2016; 89:524–526.

Rogers et al 2016
Jennifer K Rogers, Alex Yaroshinsky, Stuart J Pocock, David Stokar and Janice Pogoda. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. *Statist. Med. 2016,* 35 2195–2205

Sacks et al 2014
Sacks CA, Jarcho JA, Curfman GD. Paradigm Shifts in Heart-Failure Therapy — A Timeline. N Engl 2014; 371:989-991.

Sjöström et al 2015
Sjöström CD, Johansson P, Ptaszynska A, List J, Johnsson E. Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes. Diab Vasc Dis Res. 2015 Sep;12(5):352-8.

Soneson et al 2016
Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovasc Diabetol Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. 2016 Feb 19;15:37

Spertus et al 2005
Spertus J Am Heart J 2005. Monitoring clinical changes in patients with heart failure: A comparison of methods. Multicenter Study

Wanner et al 2016
Wanner Christoph; Inzucchi, Silvio E.; Lachin, John M; Fitchett, David; von Eynatten, Maximilian. Cardio metabolic Risk Factor Changes Observed in Diabetes Prevention Programs in US Settings: A Systematic Review and Meta-analysis. New England Journal of Medicine Vol: 375 (4) 2016 Page: 323 - 334

Zinman et al 2015
Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117-2128.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C CDISC definition for Hospitalization for heart failure and urgent heart failure visit

A **Heart Failure Event** includes hospitalization for heart failure and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.

Heart Failure Hospitalization is defined as an event that meets **ALL** of the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of HF

2. The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:

   (a) Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)

   (b) Decreased exercise tolerance

   (c) Fatigue

4. The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:

   (a) Physical examination findings considered to be due to heart failure, including new or worsened:

      (i) Peripheral edema

      (ii) Increasing abdominal distention or ascites (in the absence of primary hepatic disease)

      (iii) Pulmonary rales/crackles/crepitations

      (iv) Increased jugular venous pressure and/or hepatojugular reflux

      (v) S_3 gallop

      (vi) Clinically significant or rapid weight gain thought to be related to fluid retention

   (b) Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

      (i) Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT- proBNP) concentrations consistent with decompensation of

heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

(ii) Radiological evidence of pulmonary congestion

(iii) Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI))

OR

(iv) Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5. The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:

   (a) Augmentation in oral diuretic therapy

   (b) Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator)

   (c) Mechanical or surgical intervention, including:

      (v) Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)

      (vi) Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis)

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1. The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.
2. All signs and symptoms for HF hospitalization (ie, 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met.

3. The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Appendix D New York Heart Association (NYHA) Functional Classification

NYHA Functional Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

AstraZeneca

Clinical Study Protocol	
Drug Substance	Dapagliflozin
Study Code	D1699C00001
Version	2.0
Date	26 October 2017

Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction

Sponsor: AstraZeneca [redacted]

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

VERSION HISTORY

Version 1.0, 26 October 2016	
Initial creation	
Version 2.0, 25 October 2017	
Section	**Summary of change**
Multiple	Correcting typos, cross-references and AstraZeneca (AZ) House style.
Protocol synopsis 2.2 Secondary objectives 8.5.4 Analysis of the secondary variable(s)	Changing Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical/overall symptom score to total symptom score.
1.4 Study Design 2.4 Exploratory Objectives 4. Study plan timing of procedures 4.2.1 Visit 2, Randomisation (Day 0) 4.2.4 Visit 6 (Day 240±14)	Adding information related to the Echocardiographic Sub-study
2.3 Safety objectives 6.3.1 Time period for collection of adverse events 6.3.2.6 Adverse events (AEs) leading to amputation and AEs leading to a risk for lower limb amputations (“preceding events”)	Expanding the adverse event of interest category of amputations to also include: AEs leading to a risk for lower limb amputations (“preceding events”). This AE of interest was added based on discussion with regulatory authorities.
3.2 Exclusion criteria	Clarifying exclusion criteria number 3 and 13.

	Extending requirement for contraceptives (exclusion criteria 16), based on feedback from some regulatory authorities and to harmonise with informed consent form (ICF).
3.4 Procedures for handling incorrectly randomised patients	Clarifying text regarding how to handle incorrectly randomised patients.
3.9.1 Evaluation of volume status and investigational product (IP) dose reduction/interruption	Changing around the order of the subsections "IP dose reduction" and "Essential Treatments"
3.9.1 Evaluation of volume status and investigational product (IP) dose reduction/interruption	Clarification added to provide additional guidelines regarding essential treatment in the setting of acute worsening of heart failure (HF) or other acute situations.
4.2.7 Study closure visit (SCV)	Clarification regarding the investigator responsibility in terms of standard of care treatment after the patient stops IP.
5.1.1 Endpoint reporting overview 5.1.4 Potential renal endpoints	Removing the requirement of adjudicating potential endpoints related to estimated glomerular filtration rate (eGFR) decline. The rational for this change is that the endpoint criteria is not justifying adjudication of these events.
5.8 Echocardiographic Sub-study	An additional section has been added in order to capture information related to the echocardiographic sub-study.
6.3 Recording of adverse events (AEs) 6.3.2.2 Renal events	Clarification added based on feedback that the criteria was too vague, regarding what is considered an AE of interest in terms of renal events.
6.3 Recording of adverse events 6.3.5 Adverse events based on examination and tests	Limiting the recording of AEs to not include potential renal endpoints that are based on examination and tests, i.e., laboratory results only, unless fulfilling the serious adverse event (SAE) criteria or adverse event leading to discontinuation of IP (DAE) criteria. The reason not to record these endpoints related to laboratory findings is that protocol mandated laboratory values will be systematically analysed.
6.4.1 Reporting of SAEs considered to be potential endpoints	Limiting the event types that are being withheld from reporting to health authorities to include only HF endpoints and fatal AEs, i.e., AEs related to renal endpoints will not be withheld. The rationale for this limitation is to simplify the SAE reporting and to minimise the risk for withholding renal AEs of interest, which should be reported, and which could be confused for being a

	primary or secondary renal endpoint.
6.9 Medication Error	Adding information about Medication Error definition and reporting.
7.7.1 Prohibited medication	Clarifying that open label treatment with sodium glucose co-transporter 2 (SGLT2) in combination with IP is not allowed and that open label treatment with SGLT2 inhibitors should be avoided during the course of the study, i.e., clarifying that usage of open label treatment with SGLT2 inhibitors is not prohibited if the patient is not taking study medication but should be avoided. The rational for this update is to clarify that it is administration of an open label SGLT2 inhibition in combination with IP that is a protocol deviation and not if the patient is off IP.
7.7.2 Recording of concomitant medication	Including cardiovascular (CV) medications to be recorded in detail in the Electronic Case Report Form (eCRF) during the course of the study.
7.7.5.1 Cardiac and heart failure related procedures	An additional sub-section has been added in order to capture cardiac and heart failure related procedures.
8.5.6 Interim analysis	Clarifying that the Data Monitoring Committee (DMC) have the possibility to do more than one interim analysis of efficacy if they deem necessary, and that the stopping rule includes significance for the primary endpoint and CV Death
Appendix D	Appendix D has in the previous version been separated from the main Clinical Study Protocol (CSP) but is now incorporated for practical reasons. No changes made to the content.

PROTOCOL SYNOPSIS

Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction

International Co-ordinating Investigator

[redacted]

Study site(s) and number of patients planned

It is estimated that approximately 7000 patients at 500-600 sites in 20-25 countries will be enrolled to reach the target of approximately 4500 randomised patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2017	Phase III
Estimated date of last patient completed	Q4 2019	

Study design

This is an international, multicentre, parallel group, event-driven, randomised, double-blind, placebo-controlled study in patients with chronic heart failure with reduced ejection fraction (HFrEF), evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background regional standard of care therapy, for the prevention of cardiovascular (CV) death or reduction of heart failure (HF) events.

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.

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"])

Target patient population

The target population includes male and female patients with an established diagnosis of HFrEF for ≥2 months, and at high risk of cardiovascular death or heart failure events.

The study population will include patients with New York Heart Association (NYHA) Class II-IV HF with reduced left ventricular ejection fraction (LVEF≤40%), increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and eGFR ≥30 ml/min/1.73 m^2. Patients should be clinically stable and optimized on heart failure therapies according to local guidelines at the time of enrolment (and background standard of care therapy for type 2 diabetes when applicable). To ensure stability, doses of evidence based heart failure 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 type 2 diabetes, as the beneficial haemodynamic effects of dapagliflozin appear to be independent of the glycaemic effect, and can therefore be expected in both groups. To ensure balance between the diabetic and non-diabetic cohorts, stratification will be employed, with inclusion of at least 30% of each cohort.

Duration of treatment

This study is event driven. The anticipated duration of the study is approximately 33 months with an estimated mean treatment period for a patient of 24 months. The study closure procedures will be initiated when the predetermined number of primary endpoints are predicted to have occurred (n=844) i.e., the study end date (SED). 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 Data Monitoring Committee (DMC) review.

Investigational product, dosage and mode of administration

Patients will be randomised 1:1 to either dapagliflozin 10 mg or placebo. Every attempt should be made to maintain patients on dapagliflozin 10 mg or matching placebo during the course of the study. In addition to the preferred 10 mg dose, the 5 mg dose of dapagliflozin can be used in the study when clinically indicated. If the dose has been decreased to 5 mg, the dose should be increased back to dapagliflozin 10 mg or matching placebo as soon as, in the opinion of the investigator, the patient's condition is stable.

Statistical methods

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio of 0.80 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 844 primary endpoint events will provide a statistical power of 90% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo.

The study is event-driven. With an annual event rate of 11% in the placebo treatment group, 4500 patients are estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months.

All patients who have been randomised to study treatment will be included in the Full Analysis Set (FAS) irrespective of their protocol adherence and continued participation in the study. The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the intention to treat (ITT) principle using the FAS, using events confirmed by adjudication.

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 type 2 diabetes (T2D) status at randomisation, and adjusting for history of hospitalisation for heart failure. The p-value, hazard ratio and 95% confidence interval will be reported.

An interim analysis is planned to be performed when 75% of the primary endpoints are adjudicated, using a Haybittle-Peto rule. The interim analysis will assess superiority of dapagliflozin to placebo.

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilized. No multiplicity control is placed on the exploratory endpoints.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACE-I	Angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
AE	Adverse event
AF	Atrial fibrillation
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARB	Angiotensin receptor blockers
AST	Aspartate transaminase
AZ	AstraZeneca, sponsor
BNP	B-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CHF	Congestive Heart Failure
CABG	Coronary Artery Bypass Grafting
CDISC	Clinical Data Interchange Standards Consortium
CEA	Clinical Event Adjudication
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CRO	Clinical research organisation
CRT	Cardiac resynchronization therapy
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
DAE	Adverse event leading to discontinuation of investigational product
DGR	Dangerous Goods Regulations

Abbreviation or special term	Explanation
DKA	Diabetic ketoacidosis
DMC	Data Monitoring Committee
DMP	Data Management Plan
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
E-code	Enrolment code
eCRF	Electronic Case Report Form
ePRO	Electronic patient reported outcome
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
EQ-5D-5L	EuroQol five-dimensional five-level questionnaire
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HbA1c	Glycosylated haemoglobin
hCG	Human chorionic gonadotropin
HCP	Health care professional
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HR	Hazard ratio
IATA	International Airline Transportation Association
IB	Investigator´s Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product (dapagliflozin or matching placebo)
IRB/IEC	Institutional review board/ Independent ethics committee

Abbreviation or special term	Explanation
ITT	Intention to treat
IxRS	Interactive Voice/Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LSLV	Last Subject Last Visit
LIMS	Laboratory information management system
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MRA	Mineralcorticoid receptor antagonist
MRI	Magnetic Resonance Imaging
NB	Nota bene
NLI	National lead investigator
NSAIDs	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PGx	Pharmacogenetics research
PI	Principal Investigator
PK	Pharmacokinetic
PRO	Patient reported outcomes
PTDV	Premature treatment discontinuation visit
RAA	Renin-angiotensin-aldosterone
RAAS	Renin-angiotensin-aldosterone system
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCV	Study closure visit
SED	Study end date

Abbreviation or special term	Explanation
SGLT2	Sodium glucose co-transporter 2
SU	Sulfonylurea
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes
TIA	Transient ischemic attack
TVI	Time velocity integral
ULN	Upper limit of normal
VAD	Ventricular assistance device
VAS	Visual analogue scale
WBDC	Web Based Data Capture
WHO	Word Health Organization

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Despite advances in management and treatment of chronic heart failure (HF) with reduced ejection fraction (HFrEF), HF continues to be a major cause of mortality, initial and recurrent hospitalisations, and suboptimal quality of life. The prevalence and incidence of HF continues to increase globally. An estimated 38 million people are affected by HF worldwide (Braunwald 2015) with over 1 million hospitalisations annually in the United States and Europe (Ambrosy et al 2014). The annual global economic burden in 2012 was estimated to be $108 billion (Cook et al 2014) and is projected to increase dramatically as the population ages.

The current treatment paradigm for HF involves the simultaneous targeting of multiple pathways including the renin-angiotensin-aldosterone axis (RAA), the autonomic system, and symptomatic treatment with diuretics.

Although increased efficacy in the sacubitril/valsartan arm led to early closure of the PARADIGM-HF trial, the mortality rate remained high (McMurray et al 2014, Sacks et al 2014). Even with best possible treatment, the five year survival rate for HF is worse than for most cancers (Braunwald 2015). For patients with chronic HF, worsening symptoms require prompt medical attention, add to the burden of hospital and non-hospital settings and also have a considerable economic impact (

Ponikowski et al 2016, Okumura et al 2016).

Recently, in patients with type 2 diabetes (T2D) and high cardiovascular (CV) risk, the sodium glucose co-transporter 2 (SGLT2) inhibitor, empagliflozin (JARDIANCE™), demonstrated a marked reduction in CV mortality (38% relative risk reduction [RRR]), all-cause mortality (32% RRR) as well as 35% RRR in hospitalisation from HF compared with placebo when added to background standard of care treatment (Zinman et al 2015). In a secondary analysis of HF outcomes, empagliflozin reduced the risk of hospitalisation for HF or cardiovascular death by 28 % in patients with HF at baseline (Fitchett et al 2016).

Dapagliflozin (Forxiga™/Farxiga™) is a highly selective and reversible inhibitor of human renal SGLT2, the major transporter responsible for glucose reabsorption in the kidney. Dapagliflozin's mechanism of action results in a direct and insulin-independent elimination of glucose by the kidneys. In addition to the improved glycaemic control, the persistent loss of glucose with associated calories in the urine, results in a consistent and maintained reduction of the total body weight. Further, dapagliflozin induces a diuresis, natriuresis and a decrease in blood pressure without a concomitant increase in heart rate.

Possible mechanisms for SGLT2 inhibitor benefit in patients with heart failure could include osmotic diuresis and reductions in arterial stiffness, weight, blood pressure, serum uric acid

and albuminuria. Other potential mediators include a shift in fat oxidation and increased circulating concentrations of ketone bodies which may serve as a more efficient fuel source for the failing heart (Ferrannini et al 2016). The alterations in haemodynamics and renal physiology are attributed to glucose-independent mechanisms and can therefore be expected to be similar even in the absence of diabetes (Rajasekeran et al 2016).

Data on the effect of SGLT2 inhibition in patients without diabetes is limited. However, dapagliflozin has safely been administered in healthy volunteers over a broad dose range (up to 500 mg given as single dose) (Kasichayanula et al 2014). Dapagliflozin effectively inhibited SGLT2 also in healthy volunteers without any observed events of hypoglycaemia. Furthermore, a clinical study with canagliflozin (INVOKANA™), showed clinically relevant blood pressure and weight reductions in obese non-diabetic patients without an increased incidence of hypoglycaemia (Bays et al 2013).

Dapagliflozin has been investigated in a thorough T2D clinical development program. In addition, the trial DECLARE-TIMI58 (D1693C00001) is ongoing and includes >17,000 T2D patients with elevated CV risk to evaluate dapagliflozin 10 mg on CV outcome.

Available data from a CV outcome meta-analysis showed that dapagliflozin is not associated with increased CV risk and the results even suggested the potential for a beneficial effect on heart failure hospitalisations (Sonesson et al 2016). In a post-hoc analysis from the pooled database from the dapagliflozin development program, patients with a history of T2D and concomitant heart failure (171 patients received dapagliflozin 10 mg and 149 patients received placebo), had a significant reduction in weight, blood pressure (BP) and glycosylated haemoglobin (HbA1c) and dapagliflozin was well tolerated. Volume depletion and hypoglycaemia adverse events (AEs) were balanced between the groups (Kosiborod et al 2015). Although very few HF hospitalisation events occurred, numerically these favoured dapagliflozin vs placebo.

The aim of the proposed study is to investigate the efficacy and safety of dapagliflozin in patients with an established diagnosis of HFrEF (with or without T2D) where the prevalence and unmet needs for reducing CV mortality and heart failure events as well as improving symptoms remain high.

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for study design and population

This is a randomised, double-blind, parallel-group study. Randomisation and double blinding will minimize potential bias. This will be a multicentre study in numerous geographic regions to provide a wide applicability of results.

The target population includes male and female patients with an established diagnosis of HFrEF for ≥2 months, and at high risk of CV death or HF events.

Although patients may have been previously hospitalised for HF (but prior hospitalisation is not required) they must be clinically stable and optimized on HF therapies according to local

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.

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

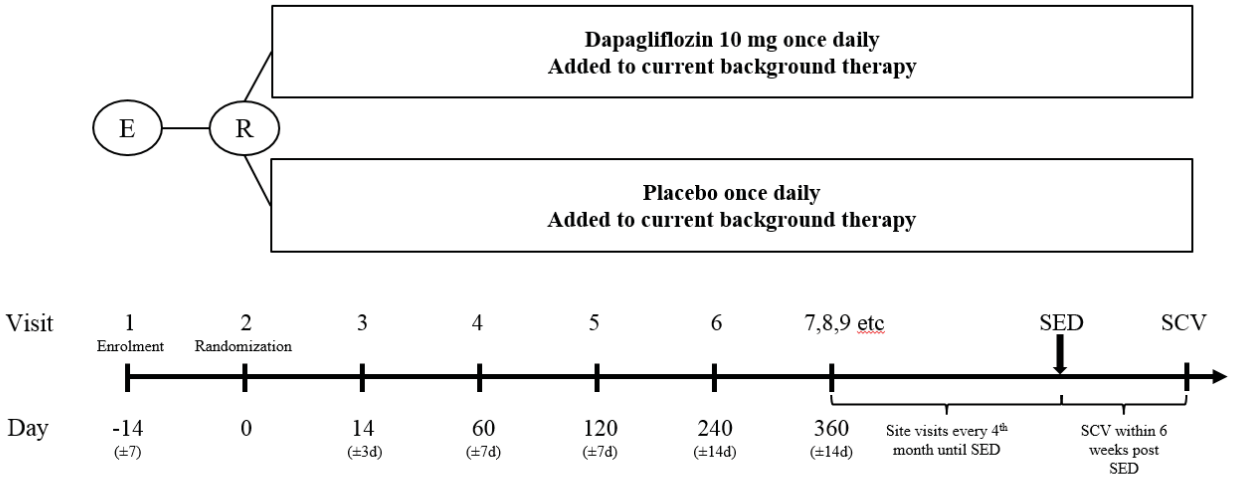
10 mg versus placebo, given once daily in addition to background standard of care therapy, for the prevention of CV death or reduction of HF events.

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.

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

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.

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

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

and

– if considered appropriate by the patient's treating physician; a mineralocorticoid receptor antagonist (MRA)

NB: Most patients with heart failure require treatment with a diuretic to control sodium and water retention leading to volume overload. It is recognized that diuretic dosing may be titrated to symptoms, signs, weight and other information and may thus vary. Each patient should, however, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual.

7. eGFR ≥30 ml/min/1.73 m^2 (CKD-EPI formula) at enrolment (visit 1)

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor

2. Type 1 diabetes mellitus (T1D)

3. Symptomatic hypotension or systolic BP <95 mmHg at 2 out of 3 measurements either at visit 1 or visit 2.

4. Current acute decompensated HF or hospitalisation due to decompensated HF <4 weeks prior to enrolment

5. MI, unstable angina, stroke or transient ischemic attack (TIA) within 12 weeks prior to enrolment

6. Coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo any of these operations after randomisation

7. Implantation of a CRT within 12 weeks prior to enrolment or intent to implant a CRT device

8. Previous cardiac transplantation or implantation of a ventricular assistance device (VAD) or similar device, or implantation expected after randomisation

9. HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy or uncorrected primary valvular disease

10. Symptomatic bradycardia or second or third degree heart block without a pacemaker

11. Any condition outside the CV and renal disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator´s clinical judgement

12. Active malignancy requiring treatment at the time of visit 1(with the exception of successfully treated basal cell or treated squamous cell carcinoma)

13. Hepatic impairment (aspartate transaminase [AST] or alanine transaminase [ALT] >3x the upper limit of normal [ULN]; or total bilirubin >2x ULN at time of enrolment). An isolated increase in bilirubin in patients with known Gilbert's syndrome is not a reason for exclusion.

14. Known blood-borne diseases such as specified in Appendix B (category A and B)

15. Severe (eGFR <30 mL/min/1.73 m^2 by CKD-EPI), unstable or rapidly progressing renal disease at the time of randomisation

16. Women of child-bearing potential (i.e., those who are not chemically or surgically sterilised or who are not post-menopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator, from the time of signing the informed consent throughout the study and 4 weeks thereafter, OR women who have a positive pregnancy test at enrolment or randomisation OR women who are breast-feeding

17. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site)

18. Previous randomisation in the present study

19. Participation in another clinical study with an IP during the last month prior to enrolment

20. Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up OR any conditions that, in the opinion of the investigator, may render the patient unable to complete the study

NB: Patients who cannot complete the electronic patient reported outcome (ePRO) assessments can still participate in the study (see Section 5.1.11.5 for details regarding the patient exclusion from the ePRO assessments during certain circumstances).

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the patient or their guardian/legal representative before any study specific procedures are performed.

2. Assign patient a unique enrolment number, beginning with 'E#', which will be used to identify the patient throughout the study. The enrolment code (E-code) will be assigned in the Interactive Voice/Web Response System (IxRS).

3. Determine patient eligibility, see Section 3.

4. At visit 2, perform the randomisation transaction in the IxRS system.

Re-enrolment one single time is allowed considering that the patient has not been previously randomised. The same E-code that the patient received at the first enrolment will be used. All enrolment assessments and procedures, including re-signing the informed consent form, should be performed again.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. Regardless of what is decided about IP, all randomised patients should remain in the study and the patients should continue to be followed up in accordance with defined study procedures.

3.5 Methods for assigning treatment groups

Randomisation to IP will be performed via IxRS at Visit 2 in balanced blocks to ensure approximate balance between the treatment groups (1:1).

The IxRS will allocate the IP through a randomisation scheme and provide the randomisation number and the appropriate Kit IDs from IP available at the study site. The randomisation codes will be computer generated and loaded into the IxRS database.

At all visits where IP is dispensed, site personnel will do a kit verification in IxRS before providing the IP bottle to the patient. Detailed instruction on how to use the IxRS system will be provided to study sites.

3.5.1 Stratification and capping

The recruitment will be continuously monitored in order to achieve adequate proportions of patient sub-populations.

3.5.1.1 Stratification

Randomisation will be stratified in IxRS based on patients with and without T2D at the time of randomisation in order to ensure approximate balance between treatment groups within each sub-population. T2D at the time of randomisation is based on:

- Established diagnosis of T2D

OR

- HbA1c more or equal to 6.5% (48 mmol/mol) shown at central laboratory test at enrolment (visit 1)

3.5.1.2 Capping

The intent is to enrol as typical cross-section of patients with HFrEF and to include representative proportions of diabetic and non-diabetic patients. The number of randomised patients with and without T2D will be monitored in order to ensure a minimum of 30% in each sub-population. Randomisation may be capped (i.e., no more patients can be randomised in a specific sub-population) if the pre-determined limit is reached.

Randomisation of patients based on geographic region will be monitored to ensure global representation. LVEF value, NYHA class and atrial fibrillation status may be capped in IxRS to avoid over- or under-representation of these patient subgroups.

3.6 Methods for ensuring blinding

The blinding of treatment is ensured by using a double-blind technique. The dapagliflozin tablets and the respective placebo tablets will be identical in size, colour, smell, and taste. The bottles with IP will be labelled with unique identification numbers.

No member of the extended AZ study team, personnel at study sites, or any clinical research organisation (CRO) handling study data will have access to the randomisation scheme during the study. The AstraZeneca (AZ) personnel or delegate generating the randomisation scheme and the Supply Chain Study Management may be able to access the randomisation scheme as appropriate.

3.7 Methods for unblinding

Individual treatment codes, indicating the randomised treatment for each patient, will be available to the investigator(s) or pharmacists from the IxRS. Instructions for code breaking/ unblinding will be described in the IxRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AZ, without revealing the treatment given to patient to the AZ personnel. It is always the investigator who decides when to unblind but it is recommended that the investigator first contacts the AZ study physician for consultation regarding the need for unblinding. If unblinding is deemed necessary, the investigator can perform the unblinding in IxRS and must document all actions taken. The number of individuals at the study site who become aware of treatment status should be kept to the absolute minimum (including keeping the patient blinded if possible). Treatment with study medication should be continued if possible.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.7.1 Unblinding for bioanalytical laboratory personnel

PK samples will be analysed at the bioanalytical laboratory only for patients on active IP. The bioanalytical laboratory will therefore have access to the treatment codes but will not share the codes with the sponsor or others involved in the study until the blinding is broken for the study after closure.

3.8 Restrictions

There are no specific dietary or activity restrictions. For restricted concomitant medications see Section 7.7.

3.9 Discontinuation of investigational product (IP)

If the patient temporarily or permanently discontinues from IP, it is important that the scheduled study visits, data collection and procedures continue according to the study protocol until study closure (see Section 3.9.3).

Patients may be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.

2. AE or other safety reasons that, in the opinion of the investigator, contraindicates further dosing with IP.

3. Severe non-compliance with the study protocol.

4. DKA, consider to temporary interrupt IP if DKA is suspected. If DKA is confirmed, IP should be discontinued permanently.

5. Positive pregnancy test (discontinue IP and notify AZ representative).

3.9.1 Evaluation of volume status and investigational product (IP) dose reduction/interruption

Dapagliflozin is a SGLT2 inhibitor which by its mechanism of action reduces the reabsorption of glucose and sodium in the proximal tubules in the kidney. SGLT2 inhibition has a mild diuretic effect and an initial haemodynamic change with an initial increase in creatinine may occur.

Unexpected acute declines in eGFR

If an unexpected, acute decline in kidney function is observed, the patient should be evaluated. Volume depletion, hypotension, inter-current medical problems and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered (the latter especially in men). Several drugs may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs (NSAIDs) and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be re-considered.

Volume depletion/hypotension

Patients with clinically relevant symptoms/signs of suspected volume depletion and/or hypotension, should have their regular medication reviewed, and consideration given to reducing the dose of, or stopping concomitant non-essential medications, as assessed on an individual basis, including diuretics and drugs that lower blood pressure (except essential treatments – see below). The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in light of the patient's symptoms and signs. In patients with heart failure, discontinuation of diuretic should only be undertaken cautiously. Hypotension may also occur with other blood pressure lowering drugs and once again the need for (and dose of) non-essential agents of this type (e.g., calcium channel blockers, alpha adrenoceptor antagonists and nitrates) should also be re-considered.

IP dose reduction

If the above mentioned measures do not lead to a resolution of clinically relevant volume depletion, hypotension and/or unexpected worsening of kidney function, a dose reduction of IP to dapagliflozin 5 mg or matching placebo may be considered and the patient's condition re-evaluated after any dose adjustment.

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.

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.

Withdrawal of consent must be ascertained and documented in writing by the investigator who must inform the AZ representative and document the withdrawal of consent in the eCRF and medical records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs reported outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment and randomisation codes cannot be reused. Withdrawn patients will not be replaced. Data generated to the time of complete withdrawal from the study will not be destroyed.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at study closure (also for patients who have withdrawn their informed consent). The investigator will therefore attempt to collect information on all patients' vital status from publicly available sources at study closure, even if informed consent has been withdrawn completely, in compliance with local privacy laws/practices.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, patients are placed at undue risk because of clinically relevant findings. The judgment may be based on recommendations from the DMC, see DMC Charter for details. The study can also be stopped based on results of the interim analysis (see Section 8.5.6).

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

The schedule of study visits and assessments is shown in Table 1 and explained further in Sections 4.1 and 4.2.

Table 1 Study plan

Activity	**Enrolment**	**Randomi-sation**	**Site visits**					**Premature treatment discontin-uation visit (PTDV)**	**Study closure visit (SCV)**	**Reference in CSP**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9 etc.**	**PTDV**	**SCV**	
Day	**-14** (±7)	**0**	**14** (±3)	**60** (±7)	**120** (±7)	**240** (±14)	**Day 360** (±14 and every 4th month)		**≤6 weeks from SED**	
Sign Informed Consent Form (ICF)	X									4.1.1
Enrolment in IxRS	X									4.1.1
Local laboratory assessment of NT-proBNP[a]	X[a]									4.1.1
Inclusion/exclusion criteria	X	X								3.1
Demography	X									4.1.1
Medical/surgical history	X									4.1.1
General physical examination	X							X	X	5.2.2
Targeted physical examination		X	X	X	X	X	X			5.2.2

Activity	**Enrolment**	**Randomi-sation**	**Site visits**					**Premature treatment discontin-uation visit (PTDV)**	**Study closure visit (SCV)**	**Reference in CSP**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9 etc.**	**PTDV**	**SCV**	
Day	**-14** (±7)	**0**	**14** (±3)	**60** (±7)	**120** (±7)	**240** (±14)	**Day 360** (±14 and every 4th month)		**≤6 weeks from SED**	
Assessment of left ventricular function[b]	X									4.1.1
Echocardiographic assessment of cardiac structure and function[c]		X				X				4.1.1 5.8
NYHA Functional Classification	X				X	X		X	X	5.1.6
Electrocardiogram (ECG)	X									5.2.3
Height	X									5.2.4.2
Vital signs *(BP, pulse and body weight)*	X	X	X	X	X	X	X	X	X	5.2.4
Pregnancy testing	X	X								4.1.1
Randomisation in IxRS		X								3.5
Concomitant medication and cardiac and HF related procedures		X	X	X	X	X	X	X	X	7.7
Central laboratory assessments[d]	X	X	X	X	X	X	X	X	X	5.2.1
PK sampling (pre-dose)[e]							X			5.4

Activity	**Enrolment**	**Randomi-sation**	**Site visits**					**Premature treatment discontin-uation visit (PTDV)**	**Study closure visit (SCV)**	**Reference in CSP**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9 etc.**	**PTDV**	**SCV**	
Day	**-14** (±7)	**0**	**14** (±3)	**60** (±7)	**120** (±7)	**240** (±14)	**Day 360** (±14 and every 4th month)		**≤6 weeks from SED**	
ePRO questionnaires[f]		X			X	X	X[f]	X	X	5.1.9
Potential endpoint events, SAEs, DAEs, AEs of interest[g]	X	X	X	X	X	X	X	X	X	5.1.1
Dispense IP (including kit verification in IxRS)/Collect IP		X[h]			X	X	X	X[i]	X[i]	7.2
IP compliance reminder		X	X	X	X	X	X			7.5
Sample for future biomarker research, optional[j]		X					X			5.7

[a] Local laboratory assessment is optional and may be used to assess eligibility (according to local routine) of NT-proBNP. If used, the ICF need to be signed before the optional assessment starts.

[b] LV assessments should be done if no assessment has been performed within 12 months prior to enrolment, or if the results of prior assessments are unavailable.

[c] Only for patients in the echocardiography substudy: A baseline echocardiographic assessment will occur after eligibility is confirmed and prior to the randomization at visit 2. A follow up echocardiogram will occur at visit 6.

[d] Central laboratory assessments include alkaline phosphatase (ALP), ALT, AST, bilirubin, blood urea nitrogen (BUN), creatinine (including eGFR assessment), haematocrit, haemoglobin (Hb), HbA1c, NT-proBNP, phosphate, potassium, and sodium, as specified in Table 2.

[e] PK samples will be collected at visit 7.

[f] PGIS, KCCQ, EQ-5D-5L will be filled in at visit 2,5,6,7 and every 12 months after visit 7, and at PTDV and SCV. PGIC will be filled in at the same visits, with exception of visit 2.

[g] SAEs will be collected from the time of informed consent throughout the study until and including the patient's last visit. Potential endpoints, DAEs, AEs leading to dose reduction and temporary interruptions and AEs of interest will be collected from randomisation throughout the study until and including the patient's last visit.

[h] IP Dispensation only

[i] IP Collection only.

[j] Blood samples for potential future biomarker research will be collected at visit 2 and visit 7 and may be analysed at the discretion of AstraZeneca. The biomarker sampling is subject to separate approval/consent by the patient and is optional.

4.1 Enrolment period

4.1.1 Visit 1, Enrolment (Day -14±7)

During enrolment period the following assessments and procedures will be completed:

- Patient signs the **ICF** before any study procedures.
  - Patients who agree to the optional sampling of blood for potential future biomarker research will provide their consent. The biomarker consent is optional and included in the main ICF.
- The patient will be **enrolled** and assigned an **E-code in IxRS**.
- **Optional local laboratory assessment**

  Failure to meet the criteria for NT-proBNP is expected to be the main reason for screen failure in this study. Therefore, sites will be allowed to perform an optional pre-study assessment, which will comprise of local assessment of NT-proBNP. Investigators will only assess patients who are potentially eligible for the study based on their medical conditions and existing therapies, and only those who are expected to meet all other entry criteria.

  Local laboratory assessment of NT-proBNP will be done according to local routine.

When the local results of NT-proBNP are available and indicate that the patient may be eligible based on the clinical judgement of the investigator, the patient may proceed to further enrolment procedures:

- The investigator reviews the **inclusion and exclusion criteria**. Patients who do not meet these criteria must not be randomised in the study.
- **Demography** (date of birth, sex, race, ethnic group) and **relevant medical and surgical history,** including smoking history, will be recorded.
- The investigator will perform a **general physical examination** (see Section 5.2.2).
- Assessment of **left ventricular function** will be performed if no assessment has been performed within 12 months prior to enrolment (preferably by an echocardiogram).
- **NYHA** Functional Classification will be evaluated.

- **ECG** will be recorded.
- **Vital signs** (BP, pulse and body weight) and **height** will be assessed and recorded.
- **Laboratory samples** will be collected and sent to central laboratory as specified in Table 2.
- **Pregnancy test** for women of child-bearing potential will be done locally with a dipstick provided by central laboratory.

4.2 Treatment period

4.2.1 Visit 2, Randomisation (Day 0)

Prior to visit 2, the investigator will review laboratory results received from the central laboratory and assess eligibility based on the laboratory results from visit 1. Patients not eligible will be considered screen failures and should not continue to visit 2.

At randomisation, the following assessments and procedures will be done:

- **PGIS, KCCQ** and **EQ-5D-5L** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will re-assess the **inclusion** and **exclusion criteria**.
- **Vital signs** will be assessed and recorded.
- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.
- **Pregnancy test** for women of child-bearing potential will be done locally with a dipstick provided by central laboratory.
- **Randomisation** to IP will be done in IxRS.
    - For stratification/capping purposes, the information whether patient has T2D or AF, LVEF value and NYHA class will be recorded in IxRS (see Section 3.5.1).
- **Concomitant medications and cardiac and HF related procedures** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.

- Patients who have consented to sampling for potential future **biomarker analysis**, will provide blood samples for this purpose.

- If the patient has experienced any **SAEs** since last visit, this will be recorded in the eCRF.

- **IP** will be dispensed via IxRS to the patient. The patient will be instructed to take the IP in accordance with protocol without interruptions and, to bring all dispensed bottles to all study visits.

- For patients who are part of the echocardiographic sub-study, a baseline echocardiogram will be obtained after eligibility is confirmed and prior to initiation of IP.

4.2.2 Visit 3 (Day 14±3) and Visit 4 (Day 60±7)

At visit 3 and visit 4, the following assessments and procedures will be done:

- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.

- **Vital signs** will be assessed and recorded.

- Any changes in relevant **concomitant medications and cardiac and HF related procedures** will be recorded, see Section 7.7.

- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.

- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.

- The patient will continue taking the study medication dispensed at the last visit. IP compliance will be discussed. The patient will be reminded to take the IP in accordance with protocol and without interruptions.

4.2.3 Visit 5 (Day 120±7)

At visit 5, the following assessments and procedures will be done:

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator.

- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.

- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medications and cardiac and HF related procedures** will be recorded.
- L**aboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- New **IP** will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be reminded to take the IP in accordance with protocol and without interruptions.

4.2.4 Visit 6 (Day 240±14)

At visit 6, the following assessments and procedures will be done:

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the Investigator.
- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.
- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medications and cardiac and HF related procedures** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- New **IP** will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be reminded to take the IP in accordance with protocol and without interruptions.

- Remind the patient that at visit 7 there will be pre-dose PK sampling. The day of visit 7 the patient must delay the intake of study medication until after the visit.

- For patients who are part of the echocardiographic sub-study a final echocardiogram will be done at visit 6.

4.2.5 Visit 7, 8, 9 etc (Day 360±14; and every 4th month ±14 days)

At visit 7 and all subsequent on-site visits until SCV, the following assessments and procedures will be done:

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator, at visit 7 and every 12 months thereafter, i.e., visit 10, 13 etc.

- The investigator will perform a **targeted physical examination** with focus on signs for HF and volume status.

- **Vital signs** will be assessed and recorded.

- Any changes in relevant **concomitant medications and cardiac and HF related procedures** will be recorded.

- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.

  - At visit 7, pre-dose, a **PK sample** will be collected. This day the patient must delay the intake of IP until after the visit. The date and time of last dose before sampling will be recorded in eCRF.

  - At visit 7, patients who have consented to sampling for potential future **biomarker analysis**, will provide blood samples for this purpose.

- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.

- **IP** will be dispensed via IxRS to the patient and drug accountability of the returned medication will be checked. The patient will be instructed to take the IP in accordance with protocol without interruptions.

4.2.6 Premature Treatment Discontinuation Visit (PTDV)

Patients who prematurely and permanently discontinue treatment with study medication should return for a PTDV, which will be done as soon as possible after last IP dose.

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **general physical examination.**
- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medications and cardiac and HF related procedures** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.
- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.
- **Drug accountability** of the returned medication will be checked.

Patients who discontinue treatment prematurely should attend all study visits according to plan, including the Study Closure Visit (SCV).

For further details regarding discontinuations from IP, please see Section 3.9.

4.2.7 Study Closure Visit (SCV)

All patients will be asked to return for a SCV when the predetermined number of primary endpoint events is anticipated, i.e., SED. All randomised patients (including any patients who have discontinued treatment with IP) should return for their SCV as soon as possible but no later than 6 weeks after the SED.

- **ePRO questionnaires** will be completed by the patient prior to any other site activities and before the patient meets the investigator.
- The investigator will perform a **general physical examination.**
- **NYHA** Functional Classification will be evaluated.
- **Vital signs** will be assessed and recorded.
- Any changes in relevant **concomitant medications and cardiac and HF related procedures** will be recorded.
- **Laboratory samples** will be collected and sent to the central laboratory as specified in Table 2.

- If the patient has experienced any **potential endpoints, SAEs, DAEs and/or AEs of interest** since the last visit, this will be recorded in the eCRF.

- The patient will return remaining IP and **drug accountability** will be checked.

After stopping IP the investigator should ensure that the patient is treated according to standard clinical practice and ascertain there is a proper medical follow-up plan in place

4.2.8 Unscheduled visits

An unscheduled visit may occur in-between scheduled visits e.g., to follow up on potential endpoint events such as re-sampling for eGFR (see Section 5.1.4).

4.3 Follow-up period (Not applicable)

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs in Rave as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA).

The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Endpoint reporting overview

Potential endpoint events will be identified using laboratory data (refer to Table 2 for laboratory assessments and timings), when questioning the patient about his/her overall health, or through information received through standard medical practice. Investigators will be encouraged to have a low threshold to submit any potential/possible event that might represent an endpoint.

The following potential endpoints will be reported and source documents submitted for central adjudication:

- All deaths

- All HF events (hospitalisations for HF or urgent HF visits)

- 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]
Haematocri[t]	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.

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.

Echocardiographic images, free of any personal health or patient identifying information except study ID, will be transmitted electronically to the study echo core laboratory.

The results of this echocardiography study will be reported separately.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all personnel involved in the study are familiar with the content of this section.

6.1 Definition of adverse events (AEs)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs. The term AE in this document refers only to the categories of events described in Section 6.3.

6.2 Definitions of serious adverse event (SAE)

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix A.

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.

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**

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.

6.7 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.

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

- 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

morning, any other time point during the day may be applied, provided the patient routinely administer the IP in approximate 24 hours intervals. The IP should not be altered (e.g., crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

If the preferred 10 mg dose is reduced to dapagliflozin 5 mg or matching placebo (see Section 3.9.1) or increased back to 10 mg or matching placebo (see Section 3.9.2), this will be done in IxRS and the dose change will be recorded in the eCRF.

Missed doses of dapagliflozin or placebo blinded study medication should not be compensated for (i.e., if a dose is missed, the next regularly scheduled dose should be taken and should not be doubled).

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All IP should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of all investigational products should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

The IP provided for this study will be used only as directed in the study protocol. The site personnel will account for all IP dispensed to and returned from the patient.

Patients will be asked to bring all unused study medication and empty packages to the study site at each site visit. The investigator or delegate will enter the amount of returned tablets in the eCRF. Any patient found to be noncompliant would be counselled on the importance of taking their study medication as prescribed.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

The investigator will retain the returned medication until the AZ representative or delegate collects it, along with any medication not dispensed. The AZ representative or delegate is responsible for confirming the investigator or delegate has recorded the quantities of returned and unused tablets at a patient level before medication is destroyed. The AZ representative or delegate will advise on the appropriate method for destruction of unused study medication.

7.7 Concomitant medications and other treatments

All patients should be treated according to regional standard of care for HF, CV risk factors (e.g., blood pressure, lipids, antithrombotic treatment) and diabetes. Background medication will not be provided by the Sponsor.

7.7.1 Prohibited medication

Concomitant treatment (i.e., treatment in combination with IP) with open label SGLT2 inhibitors eg, dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and fix dose combinations containing these drugs is prohibited. Also in situations when the patient is not on IP, treatment with open label SGLT2 inhibitors during the study, could interfere with the interpretation of study results and should therefore not be given unless all other possibilities to treat the patient properly has been considered.

7.7.2 Recording of concomitant treatment

Detailed recording of medications related to HF (see Section 7.7.3), diabetes (see Section 7.7.4) as well as other relevant cardiovascular medications (e.g., statins, antihypertensive and antithrombotic agents) will be made throughout the study. In addition, all concomitant medications will be recorded at the time of any SAEs, potential endpoints and AEs of interest (as defined in section 6.3.2 and 6.4). Also, cardiac and heart failure related procedures will be captured during the study (see Section 7.7.5.1). Recording of other concomitant medications will be made at randomisation (visit 2) and at SCV.

7.7.3 Heart failure (HF) medications

To be eligible, the patient should be on background standard of care therapies for HF according to local guidelines. Standard evidence based treatments will include either an ACE inhibitor, ARB or sacubitril/valsartan in combination with a beta-blocker, as well as an MRA where appropriate unless contraindicated or not tolerated. If the patient for any reason is not on background standard of care medications at baseline, the reason for this will be recorded in the eCRF.

Most patients will also require a diuretic, generally a loop diuretic such as furosemide, to control symptoms. Optimization of volume status, and proactive adjustment of diuretic doses may help minimize any deleterious effects on hypovolemia/volume depletion accentuated by the diuretic effects of the IP.

Patients should remain on stable doses of medications which will allow assessment of incremental dapagliflozin effect. Dose reduction or discontinuation of proven effective therapies should be avoided unless all other measures fail to improve the patient's situation. In heart failure, use of ACE-I/ARBs, Sacubitril/Valsartan, mineralocorticoids and beta-blockers is supported by evidence from previous clinical trials. However, if the patient's condition warrants a change in any of these standard evidence based medications, it will be allowed at the discretion of the investigator. If patients require dose adjustment of background therapy to avoid signs/symptoms of volume depletion, diuretics should be decreased prior to adjusting other medications.

7.7.4 Anti-diabetes treatment

7.7.4.1 Background

More than 40% of patients with established HF are estimated to have T2D (Kristensen et al 2016) and it is expected that a large proportion of patients in this study will have an established diagnosis of T2D when included in this study. Furthermore it is expected that some patients will develop T2D during the course of the study. Treatment of diabetes should follow established guidelines, according to glycaemic goals as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) in their joint Position Statement (Inzucchi et al 2012, Inzucchi et al 2015). In brief, the ADA/EASD recommends lowering HbA1c to < 7.0% in most patients. Less stringent HbA1c goals, e.g., 7.5 to 8% or even slightly higher may be appropriate for patients with a history of severe hypoglycaemia, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counselling, and effective doses of multiple glucose-lowering agents, including insulin.

7.7.4.2 Treatment of patients with established diagnosis of type 2 diabetes

Patients with T2D at randomisation will continue their T2D treatment. Patients are eligible for adjustments in their anti-diabetes treatment at the discretion of their diabetes health care provider. Diabetes medications at baseline and any changes throughout the study, will be recorded in the eCRF.

7.7.4.3 Use of medications known to cause hypoglycaemia in type 2 diabetes

Insulin and insulin secretagogues are known to cause hypoglycaemia. Therefore, patients treated with insulin or SU have a higher risk of experiencing hypoglycaemic events compared with those treated with other antidiabetic agents. Therefore a lower dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia when used in combination with study medication.

Reduction of insulin by 10-20% (total daily dose) and SU by 25- 50% and increased frequency of blood glucose monitoring may be considered in patients receiving insulin and/or SU and with baseline HbA1c <7% at randomisation.

7.7.5 Other concomitant treatment

Medications other than described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF as applicable.

7.7.5.1 Cardiac and heart failure related procedures

During the course of the study, information will be recorded regarding any cardiac and heart failure related procedures in a specific eCRF module. The procedures will be collected from time of randomisation to SCV. Procedures include but are not limited to: PCI/CABG, pacemaker implantation, mechanical fluid removal etc.

7.8 Post Study Access to Study Treatment

Post-study treatment will not be provided by the Sponsor.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violations have been identified and documented.

A comprehensive Statistical Analysis Plan (SAP) will be developed prior to first patient randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

The results of the key study outcome will be independently validated by an external statistical team.

8.2 Sample size estimate

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio (HR) of 0.80 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 844 primary endpoint events will provide a statistical power of 90% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The study is event-driven. The assumed HR of 0.80 is considered as clinically relevant and has taken into account the HF outcomes in the EMPA-REG trial.

With an annual event rate of 11% in the placebo treatment group, 4500 patients are estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months. The assumed placebo event rate of 11% is based on a review of recently published clinical studies in the HFrEF population, including the PARADIGM-HF trial. This study is a group sequential design study with one interim analysis using Haybittle-Peto boundary (a one-sided alpha=0.001), leaving a one-sided alpha of 2.496% for the final analysis. In addition, the expected number of patients who will be lost to follow-up is expected to be small; hence, these are not considered in the determination of the sample size.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

All patients who have been randomised to study treatment will be included in the Full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised IP assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

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

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

train them in any study specific procedures and the WBDC, ePROs system and other relevant systems utilised.

The PI will ensure that appropriate training relevant to the study is given to all site personnel, and that any new information relevant to the performance of this study is forwarded to the personnel involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other personnel).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s) and site personnel.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., medical records).
- Perform source data review, i.e., review of source documentation to check quality of source, review protocol compliance, ensure critical processes and source documentation are adequate.
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other personnel at the centre needs information and advice about the study conduct.

9.2.1 Risk based quality management

Quality by design will be implemented, including a focus on identifying key risks to patient safety, data quality, and Good Clinical Practice (GCP)/regulatory compliance, to build quality into the design, conduct, analysis and reporting of the study.

A risk based monitoring approach will be applied for this study. A mix of monitoring strategies will be implemented: on-site monitoring, remote monitoring (site level monitoring activities performed at a location other than the study site) and centralized monitoring systems. Monitoring strategies will be tailored to risks, permit timely oversight (through central/remote monitoring and use of technology), and will be focused on critical processes and critical data.

Central monitoring will be used to check that data is consistent and complete, identify unusual distribution of data, identify higher risk sites to target additional monitoring, and to ensure routine review of data is completed in real time.

9.2.2 Source data

The Clinical Study Agreement (CSA) will specify the location of source data. The investigator must provide direct access to source data/documents for monitoring, audits, Institutional Review Board/Independent Ethics Committee (IRB/IEC) review, and regulatory inspections.

9.2.3 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AZ and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.4 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last patient undergoing the study’.

The study is expected to start in Q1 2017 and to end by Q4 2019.

The study may be terminated at individual study sites if the study procedures are not being performed according to GCP, or if recruitment is slow. AZ may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

9.4 Data management by AstraZeneca

Data management will be performed by AZ Data Management Centre personnel at Cognizant, according to the Data Management Plan (DMP).

Data entered into the eCRF will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be reviewed, queried and updated as needed.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug-Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

The data will be validated as defined in the DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

9.5 Serious Adverse Event (SAE) Reconciliation

SAE reconciliation will be done between the study database and safety database.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AZ policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Institutional review board/ Independent ethics committee (IRB/IEC) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site personnel.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The IRB/IEC should approve all advertising used to recruit patients for the study.

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.

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.

Bays et al 2013
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.

Ferrannini et al 2016
Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care 2016 Jul; 39(7):1108-14.

Fitchett et al 2016
Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J 2016 May 14;37(19):1526-34.

Ghosh and Lin 2000
Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. Biometrics 2000; 56:554–562.

Green et al 2000
Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: A New Health Status Measure for Heart Failure. J Am Coll Cardiol. 2000 Apr;35(5):1245-55.

Hicks et al 2014
Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL et al, on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for Clinical Data Interchange Standard Consortium (CDISC) August 20, 2014.

Inzucchi et al 2012
Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.

Inzucchi et al 2015
Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck Met al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015 Jan;38(1):140-9.

Kasichayanula et al 2014
Kasichayanula S, Liu X, Lacreta F, Griffen SC, Boulton DW. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. Clin Pharmacokinet. 2014 Jan;53(1):17-27.

Kohan et al 2014
Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin educes weight and blood pressure but does not improve glycemic control. Kidney Int. 2014 Apr;85(4):962-71.

Kosiborod et al 2015
Kosiborod M, Gause-Nilsson I, Xu J, Sonesson C, Johnsson E. Efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus and Concomitant Heart Failure. J Diabetes Complications. Published online: 2017 Feb 10. doi: 10.1016/j.jdiacomp.2017.02.001.

Kosiborod et al 2016
Kosiborod M, Xu J, Sjostrand M, Sjostrom CD. Safety and Efficacy of Dapagliflozin in Combination with Potassium-sparing Agents. American Diabetes Association, June 2016, New Orleans. Abstract 1094-P.

Kristensen et al 2016
Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B et al. Risk related to pre–diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail. 2016 Jan;9(1).

Levey at al 2009
Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5; 150(9):604-12.

Lin et al 2000
Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 2000; **62**(4):711–730.

McMurray et al 2014
McMurray JJ, Packer M, Desai AS, Gong JG, Lefkowitz MP, Rizkala AR et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Eng J Med 2014; 371:993-1004.

Okumura et al 2016
Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL et al for the PARADIGM-HF Investigators and Committees. Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting: Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) Circulation 2016;133:2254-62.

Ponikowski et al 2016
Ponikowski P, Voors A, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. European Heart Journal 2016:18, 891–975.

Rajasekeran et al 2016
Rajasekeran H, Lytvyn Y, Cherney DZI. Sodium–glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis. Kidney International 2016; 89:524–526.

Rogers et al 2016
Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. Stat Med. 2016 Jun 15;35(13):2195-205.

Sacks et al 2014
Sacks CA, Jarcho JA, Curfman GD. Paradigm Shifts in Heart-Failure Therapy — A Timeline. N Engl 2014; 371:989-991.

Sjöström et al 2015
Sjöström CD, Johansson P, Ptaszynska A, List J, Johnsson E. Dapagliflozin lowers blood pressure inhypertensive and non-hypertensive patients with type 2 diabetes. Diab Vasc Dis Res. 2015 Sep;12(5):352-8.

Sonesson et al 2016
Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. Cardiovasc Diabetol 2016 Feb 19;15:37.

Spertus et al 2005
Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J. 2005;150:707-15.

Wanner et al 2016
Wanner Christoph; Inzucchi, Silvio E.; Lachin, John M; Fitchett, David; von Eynatten, Maximilian. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016;375:323-34.

Zinman et al 2015
Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117-2128.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasia (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca (AZ) would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Clinical data interchange standards consortium (CDISC) definition for Hospitalisation for heart failure (HF) and urgent heart failure visit

A **Heart Failure Event** includes hospitalisation for heart failure and may include urgent outpatient visits. HF hospitalisations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalisations.

Heart Failure Hospitalisation is defined as an event that meets **ALL** of the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of HF
2. The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)
3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
   - (a) Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   - (b) Decreased exercise tolerance
   - (c) Fatigue
4. The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:
   - (a) Physical examination findings considered to be due to heart failure, including new or worsened:
     - (i) Peripheral edema
     - (ii) Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
     - (iii) Pulmonary rales/crackles/crepitations
     - (iv) Increased jugular venous pressure and/or hepatojugular reflux
     - (v) S_3 gallop
     - (vi) Clinically significant or rapid weight gain thought to be related to fluid retention
   - (b) Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

(i) Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT- proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

(ii) Radiological evidence of pulmonary congestion.

(iii) Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)).

OR

(iv) Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5. The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:

   (a) Augmentation in oral diuretic therapy

   (b) Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator)

   (c) Mechanical or surgical intervention, including:

      (v) Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)

      (vi) Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1. The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalisation.

2. All signs and symptoms for HF hospitalisation (i.e., 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met.

3. The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Appendix D New York Heart Association (NYHA) Functional Classification

NYHA Functional Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix E Patient Reported Outcome (PRO) questionnaires

E1 Patient Global Impression of Severity (PGIS) for Heart Failure Symptoms

Study Number: D1699C00001		Site Number:
Subject Number:	Visit Number:	Assessment Date:

Patient Global Impression of Severity for Heart Failure Symptoms

Overall, how would you rate the severity of your heart failure symptoms today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

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

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
☐	☐	☐	☐	☐	☐

3. Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you? It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all Bothersome	I've had no swelling
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your fatigue bothered you? It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no fatigue
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the <u>past 2 weeks,</u> how much has your shortness of breath bothered you?
It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath
□	□	□	□	□	□

9. Over the <u>past 2 weeks,</u> on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
□	□	□	□	□

10. Heart failure symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your heart failure gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure
□	□	□	□	□

11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
□	□	□	□	□

12. Over the <u>past 2 weeks</u>, how much has your heart failure limited you enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all
□	□	□	□	□

13. If you had to spend the rest of your life with your heart failure the way it is <u>right now</u>, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
□	□	□	□	□

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?

I felt that way all of the time	I felt that way most of the time	I occasionally felt that way	I rarely felt that way	I never felt that way
☐	☐	☐	☐	☐

15. How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 week?

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

Activity	Severely Limited	Limited quite a bit	Moderately Limited	Slightly Limited	Did not limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationship with loved ones	☐	☐	☐	☐	☐	☐

E4 EuroQol five-dimensional five-level questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

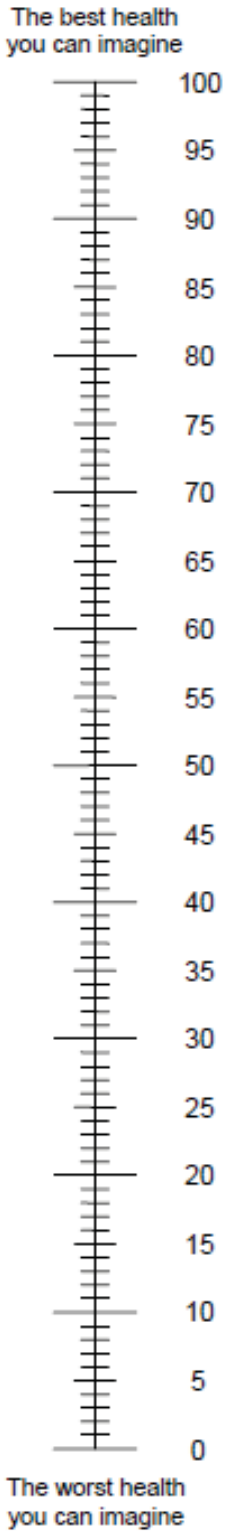
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Document Name:	Clinical Study Protocol HF
Document Title:	D1699C00001 Clinical Study Protocol Version 1
Document ID:	Doc ID-003203568
Version Label:	3.0 Approved CURRENT LATEST

Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)	**Signed By**	**Meaning of Signature**
26-Oct-2017 16:15 GMT+0100	[redacted]	Clinical Approval
26-Oct-2017 20:14 GMT+0100	[redacted]	Biostatistics Approval
26-Oct-2017 22:46 GMT+0100	[redacted]	Clinical Operations Approval
27-Oct-2017 07:16 GMT+0100	[redacted]	Clinical Development Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.

AstraZeneca

Statistical Analysis Plan

Study Code	D1699C00001
Edition Number	1.0
Date	31/January/2017

Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction
