Clinical Study Protocol	
Drug Substance	Dapagliflozin
Study Code	D169CC00001
Version	1.0
Date	24th April 2018

An International, Double-blind, Randomised, Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

DELIVER - Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

VERSION HISTORY

Version 1.0, 24th April 2018
Initial creation

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Study of Assessments

Visit	1 Enrolment	2 Randomisation	3	4	5	6	7 – onwards	Premature Treatment Discontinuation Visit	Study Closure Visit	For details see Section:
Day/Month	**Day -21 to Day -1**	**Day 1**	**Day 30 (±7)**	**Day 120 (±7)**	**Day 240 (±7)**	**Day 360 (±7)**	**Day 480 - onwards (every 120 days ±14 days)**		**≤ 6 weeks after PACD**	
Informed consent	X[6]									5.1, A 3
Inclusion/exclusion criteria	X	X								5.1, 5.2
Demographics	X									5.15.1
Medical history	X	X								5.15.1
Concomitant medication		X	X	X	X	X	X	X	X	6.5
Cardiac and HF related procedures			X	X	X	X	X	X	X	8.5.1.4
Physical exam	X	X							X	8.4.1
Systolic and diastolic BP	X	X	X			X	X[3]	X	X	5.2, 8.4.2
Pulse	X	X	X			X	X[3]	X	X	5.2, 8.4.2
Weight	X					X	X[3]	X	X	8.4.6.1
Height	X									8.4.6.1
NYHA classification	X	X	X	X	X			X	X	5.1, Appendix J
12-lead ECG	X									8.4.3

Visit	**1 Enrolment**	**2 Randomisation**	**3**	**4**	**5**	**6**	**7 – onwards**	**Premature Treatment Discontinuation Visit**	**Study Closure Visit**	**For details see Section:**
Day/Month	**Day -21 to Day -1**	**Day 1**	**Day 30 (±7)**	**Day 120 (±7)**	**Day 240 (±7)**	**Day 360 (±7)**	**Day 480 - onwards (every 120 days ±14 days)**		**≤ 6 weeks after PACD**	
C-lab NT-proBNP	X									5.1
C-lab eGFR (creatinine)	X		X	X		X	X[3]			5.2, 8.4.4
C-lab HbA1c	X									6.3.1.1
Sample for genetic research, if applicable[5]		X								Appendix D
KCCQ		X[4]	X[4]	X[4]	X[4]			X[4]	X[4]	8.3.3.1
PGIS		X[4]	X[4]	X[4]	X[4]			X[4]	X[4]	8.3.3.2
EQ-5D-5L		X[4]			X[4]			X[4]	X[4]	8.3.3.3
Local pregnancy test (female patients with childbearing potential only)		X								5.1
Randomisation		X								8.2.1
Dispense investigational product (IP)		X		X	X	X	X			6
Collect unused IP; check IP compliance				X	X	X	X	X	X	6

Visit	**1 Enrolment**	**2 Randomisation**	**3**	**4**	**5**	**6**	**7 – onwards**	**Premature Treatment Discontinuation Visit**	**Study Closure Visit**	**For details see Section:**
Day/Month	**Day -21 to Day -1**	**Day 1**	**Day 30 (±7)**	**Day 120 (±7)**	**Day 240 (±7)**	**Day 360 (±7)**	**Day 480 - onwards (every 120 days ±14 days)**		**≤ 6 weeks after PACD**	
Efficacy events (death and worsening heart failure) [1]		X[1]	X	X	X	X	X	X	X	8.3
Safety events[2]	X	X	X	X	X	X	X	X	X	8.4

AEs Adverse events; DAEs Adverse events leading to discontinuation of investigational product; PACD Primary Analysis Censoring Date; SAEs Serious adverse events; C-lab Central laboratory

[1] Efficacy events are considered as endpoints from time of randomisation and throughout the study. Prior to randomisation, these events are considered as SAEs.

[2] SAEs will be recorded from the time of informed consent. DAEs and Amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs will be recorded from Visit 2 onwards.

[3] Assessments to be repeated every 12 months.

[4]Will be administered using a site-based electronic device. It is preferred that PRO questionnaires are completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions

[5]Blood sample for future genetic research is optional. The genetic sampling is subject to separate consent by the patient.

[6] The Patient signs the ICF. Patients who agree to the optional sampling of blood for genetic research will provide their consent.

1.2 Synopsis

International coordinating Investigator

Scott D. Solomon, MD

[redacted]
Harvard Medical School
[redacted]
Brigham and Women´s Hospital
75 Francis Street
Boston, MA 02115
US

Protocol Title:

An International, Double-blind, Randomised Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF).

Rationale:

The prevalence of chronic heart failure (HF) continues to increase globally, and the annual global economic burden (several hundred billion dollars in 2012) will increase as the population ages. Approximately half of all heart failure patients have heart failure with preserved ejection fraction (HFpEF) representing a particularly significant unmet need given that no approved pharmacotherapy exists specifically for this condition. Patients with HFpEF generally receive diuretic treatment for symptom relief, and should receive guideline recommended therapies for concomitant diseases such as hypertension. Recent data from cardiovascular (CV) outcome trials of SGLT2 inhibitors (empagliflozin and canagliflozin) and real world studies (including patients treated with dapagliflozin) indicate that treatment with SGLT2 inhibitors can reduce the risk of CV death and hospitalisation due to HF in patients with Type 2 Diabetes (T2D) overall and in patients with T2D and concomitant HF. Limitations associated with the randomised clinical trials as well as the observational studies are that only patients with T2D were studied, and that the proportion of patients with HFrEF and HFpEF, respectively, is unknown. This study will test the hypothesis that dapagliflozin will reduce the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function (LVEF >40%), with or without T2D.

Table 2 Objectives and Endpoints

Primary objective:	Endpoint/variable:
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function.	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF 3. Urgent HF visit (e.g., emergency department or outpatient visit)
Secondary objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in reducing the total number of recurrent HF hospitalisations and CV death	Total number of (first and recurrent) hospitalisations for HF and CV death
To determine whether dapagliflozin is superior to placebo in improving Patient Reported Outcomes measured by KCCQ	Change from baseline in the total symptom score (TSS) of the KCCQ at 8 months
To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA class	Proportion of patients with worsened NYHA class from baseline to 8 months
To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality	Time to the occurrence of death from any cause
Safety objective:	**Endpoint/variable:**
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF	Serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs), amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs
Exploratory Objective:	**Endpoint/Variable:**
To determine whether dapagliflozin is superior to placebo in reducing all-cause hospitalisation	Time to the first occurrence of hospitalisation from any cause
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 compare the effect of dapagliflozin versus placebo on health status assessed by Patient global impression of severity (PGIS) questionnaires	Changes in health status measured by PGIS
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 have an effect on eGFR.	Change in eGFR from baseline
To explore whether dapagliflozin compared to placebo improves KCCQ summary scores, subscores of TSS (Symptom frequency and symptom burden) and domains	Change in Clinical summary score, TSS sub-scores, Overall summary score, QoL score
To collect and store blood samples for future exploratory genetic research	Not applicable. Results will be reported separately

BP Blood pressure; CV Cardiovascular; EQ-5D-5L EuroQol five-dimensional five-level questionnaire
HF Heart failure; HFrEF Heart failure with reduced ejection fraction; KCCQ Kansas City Cardiomyopathy Questionnaire NYHA New York Heart Association

Overall design:

This is an international, multicentre, parallel-group, event-driven, randomised, double-blind study in patients with HFpEF, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background regional standard of care therapy, including treatments to control co-morbidities, in reducing the composite of CV death and heart failure events (hospitalisations for HF or urgent HF visits). Adult patients aged ≥40 years with HFpEF (LVEF >40% and evidence of structural heart disease) and New York Heart Association (NYHA) class II-IV who are eligible according to the inclusion/exclusion criteria will be randomised in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo. Both out-patients and in-patients hospitalised for heart failure and off intravenous heart failure-therapy for 24 hours can be randomised. It is estimated that approximately 8000 patients at approximately 400-500 sites in 20-25 countries will need to be enrolled to reach the target of approximately 4700 randomised patients.

Study Period:

Estimated date of first patient enrolled: Q3 2018

Estimated date of last patient completed: Q3 2021

Number of randomised Subjects: approximately 4700 patients

Treatments and treatment duration:

Patients will be randomised in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo once daily. The anticipated average treatment duration is 24 months (range 15 to 33 months).

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will review accumulating trial data by treatment group in order to monitor patient safety and efficacy, ensure the validity and integrity of the trial, and make benefit-risk assessment.

Statistical methods

This study is event-driven. The primary objective of the study is to determine the superiority of dapagliflozin versus placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit). Assuming a true hazard ratio (HR) of 0.80 between dapagliflozin and placebo, using a two-sided alpha of 5%, 844 primary endpoint events will provide a statistical power of 90% for the test of the primary composite endpoint.

Approximately 4700 patients are estimated to provide the required number of primary events during an anticipated recruitment period of 18 months and a minimal follow-up period of 15 months (total study duration 33 months, average follow-up 24 months). Randomisation will be stratified by presence or absence of Type 2 Diabetes (T2D).

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, including events occurring on or prior to the primary analysis censoring date (PACD), 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. The p-value, hazard ratio and 95% confidence interval will be reported.

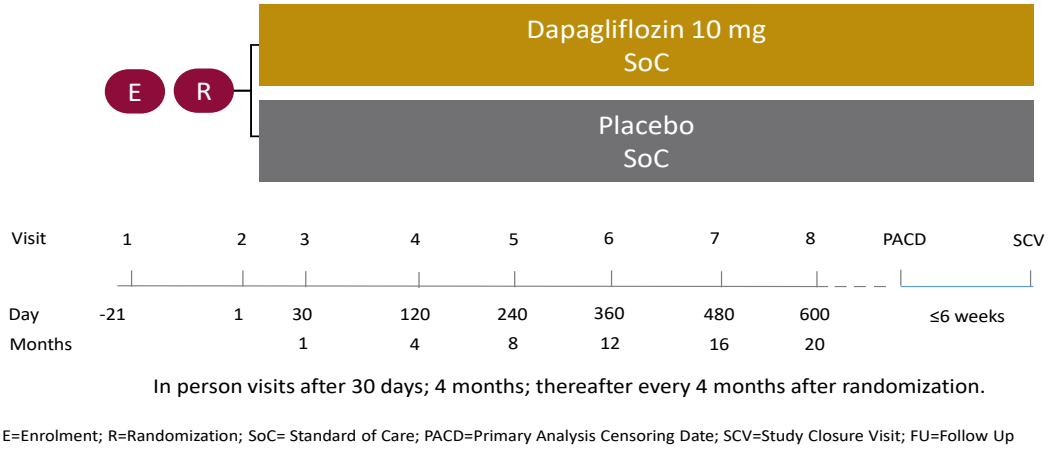
Interim analysis of superiority and futility is planned to be performed including approximately 67% of target number of adjudicated primary endpoints.

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.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



E=Enrolment; R=Randomization; SoC= Standard of Care; PACD=Primary Analysis Censoring Date; SCV=Study Closure Visit; FU=Follow Up

2. INTRODUCTION

2.1 Study rationale

The prevalence of chronic HF continues to increase globally. An estimated 38 million people are affected worldwide (Braunwald 2015), with over 1 million hospitalisations annually in both 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); this will increase dramatically as the population ages.

Heart failure is a complex syndrome caused by structural and/or functional abnormalities. It is characterised by dyspnoea, fatigue, and pulmonary congestion and/or peripheral oedema due to fluid retention. Patients with signs and symptoms of HF are categorised, based on measurement of left-ventricular ejection fraction (LVEF), as having HF with reduced LVEF (HFrEF) or HF with preserved LVEF (HFpEF).

Approximately half of all heart failure patients have HFpEF (Oktay et al 2013). Risk of death for HFpEF patients is high, with annualised mortality rate up to 15% in community settings (Lam et al 2011). In controlled clinical trials, patients with HFpEF tend to be older and have a higher prevalence of hypertension as compared to patients with HFrEF, although major clinical outcomes are similarly dominated by CV death and HF hospitalisation, the yearly event rates appear to be lower than in HFrEF (Solomon et al 2005). However, patients with HFpEF have a particularly significant unmet medical need given that outcome studies hitherto performed have not resulted in any approved pharmacotherapy specifically for this condition. Conversely, outcome studies have provided evidence for treatments for HFrEF that hence can improve symptoms and haemodynamics as well as reduce hospitalisations for heart failure and mortality. These treatments include diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin II receptor blocker neprilysin inhibitors, mineralocorticoid receptor antagonists, and beta-blockers (Iwaz et al 2016).

Recent data from cardiovascular (CV) outcome trials of SGLT2 inhibitors (empagliflozin and canagliflozin) indicate that treatment with SGLT2 inhibitors can reduce the risk of CV death and hospitalisation due to HF in patients with T2D overall, and in patients with T2D and concomitant HF (Zinman et al 2015; Fitchett et al 2016; Neal et al 2017; Rådholm et al 2018).

Results from real-world observational studies are broadly consistent with the randomised clinical trials in supporting the benefits of SGLT2 inhibitors in reducing risk of HF hospitalisation and CV death. The CVD-REAL study, consisting of more than 300000 patients with T2D, both with and without established CV disease, across 6 countries found that patients treated with SGLT2 inhibitors compared to patients treated with other glucose lowering drugs was associated with a relative risk reduction in hospitalisation due to HF (39%), all-cause death (51%), and the composite of hospitalisation due to HF or CV death (46%) (Kosiborod et al 2017a).

Limitations associated with the randomised clinical trials as well as the observational studies are that only patients with T2D were studied, and that the proportion of patients with HFrEF and HFpEF, respectively, is unknown.

This study will test the hypothesis that dapagliflozin is superior to placebo in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function (LVEF >40%), with or without T2D.

2.2 Background

Dapagliflozin is a potent, highly selective and orally active inhibitor of human renal SGLT2. A detailed description of the chemistry, pharmacology, efficacy, and safety of dapagliflozin is provided in the Investigator's Brochure. Supporting the hypothesis that dapagliflozin may reduce CV Death and HF events in HF patients, irrespective of diabetes status, are observations 'from the overall dapagliflozin clinical development programme. Dapagliflozin lowers HbA1c with a low risk of inducing hypoglycaemia. In addition, dapagliflozin treatment has also been shown to reduce weight and systolic blood pressure, and to have favourable effect on increased blood uric acid, albuminuria, and arterial elasticity, conditions which are associated with increased CV and renal risk (Shigiyama et al 2017). Dapagliflozin is believed be nephroprotective through non-glycaemic mechanisms (Wanner et al 2016).

The identified blood pressure lowering effects, may reduce the primary outcome in a study population with high prevalence of hypertension, similarly, the observed effects on body weight, may be beneficial to the large part of the study population with obesity. The findings from EMPA-REG, with a similar SGLT2 inhibitor compound, suggests that kidney function is preserved, or improved in this diabetic study population. Furthermore, HFpEF patients are characterized by fluid retention and a change in cardiac metabolism favouring glucose as substrate, both of which has been hypothesised to be positively impacted by SGLT2 inhibitor treatment. Moreover, arterial stiffness, and abnormal ventriculo-arterial coupling, are common in patients with HFpEF, and may be modified by SGLT2 inhibitor treatments.

The clinical studies in healthy subjects at high multiple doses also show that, due to the mechanism of action, dapagliflozin does not induce hypoglycemia in nondiabetic subjects; however, pharmacodynamic effects on glucose, sodium, and urinary volume are observed. Therefore, the changes in these diabetes-independent mechanisms and intrarenal physiology are expected to be similar regardless of underlying disease.

This study is an international, multicentre, parallel-group, event-driven, randomised, double-blind, placebo-controlled study in HFpEF patients, evaluating the effect of dapagliflozin 10 mg, given once daily in addition to background regional standard of care therapy, including treatments to control co-morbidities, in reducing the composite of CV death and heart failure events (hospitalisations for HF or urgent HF visits).

2.3 Benefit/risk assessment

Dapagliflozin has global marketing approval in 44 countries with the most recent estimate of cumulative post-marketing experience totalling over 1.6 million patient-years. Detailed information about the known and expected benefits and risks and reasonably expected adverse events of dapagliflozin appears in the Investigator's Brochure. The following is a summary of benefit-risk considerations relevant to the HFpEF target population.

2.3.1 Potential risks to patients

Dapagliflozin reduces blood volume and blood pressure from its diuretic effect, which could be a concern in patients with HFpEF, but also be important mechanisms of a potential treatment effect. However, in the dapagliflozin type 2 diabetes mellitus (T2D) program, the rate of events related to volume depletion and impaired renal function have been similar between dapagliflozin and placebo. Loop-diuretics are widely used in the target patient population and are also allowed in this study. A pooled analysis of patients with T2D and HF in the dapagliflozin development program, showed no increase of volume depletion events but increase in renal events, mainly creatinine increases, in patients treated with dapagliflozin (n=171) compared with placebo treated patients (n=149). About half of the patients were on loop diuretics (Kosiborod et al 2017b).

An increase in amputations, mostly affecting toes, was observed in a clinical trial (Neal et al 2017) with another SGLT2 inhibitor. There is no indication from the clinical development program that dapagliflozin is associated with an increased risk of amputation (see Section 8.5.1.1 for the detection and capture of amputation events).

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.

There have been post-marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with T2D taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected interruption of dapagliflozin treatment should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., T1D, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in patients in these circumstances. Dapagliflozin is currently not indicated for the treatment of patients with T1D; these patients are excluded from this study.

2.3.1.1 Protection against risks

This study has been designed with appropriate measures in place to monitor and minimise any potential risks to participating patients. Data regarding amputations and adverse events potentially placing the patient at risk for a lower limb amputation will be collected (see Section 8.5.1.1). 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 (see Section 9.5.1).

2.3.2 Potential benefits to patients

All patients in the study are expected to be optimally treated according to regional standard of care therapy, including treatments to control co-morbidities, and dapagliflozin or placebo will be administered on top of this treatment.

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.

2.3.3 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 eligible patients. Although hypothesis-generating data suggest beneficial effects of SGLT2 inhibitors in patients with T2D with heart failure, at the time of writing of this clinical study protocol, no available SGLT2 inhibitor has a treatment indication for patients with HFpEF. The proposed clinical study will test the hypothesis that dapagliflozin reduces the risk of CV death and HF events in patients with HFpEF, with or without T2D, in a rigorous fashion. The results could potentially offer substantial benefit to patients with HFpEF, a patient population with a large medical need for effective treatments.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function.	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF 3. Urgent HF visit (e.g., emergency department or outpatient visit)
Secondary objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in reducing the total number of recurrent HF hospitalisations and CV death	Total number of (first and recurrent) hospitalisations for HF and CV death
To determine whether dapagliflozin is superior to placebo in improving Patient Reported Outcomes measured by KCCQ	Change from baseline in the total symptom score (TSS) of the KCCQ at 8 months
To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA class	Proportion of patients with worsened NYHA class from baseline to 8 months

To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality	Time to the occurrence of death from any cause
Safety objective:	**Endpoint/variable:**
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF	Serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs), amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs
Exploratory Objective:	**Endpoint/Variable:**
To determine whether dapagliflozin is superior to placebo in reducing all-cause hospitalisation	Time to the first occurrence of hospitalisation from any cause
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 compare the effect of dapagliflozin versus placebo on health status assessed by Patient global impression of severity (PGIS) questionnaires	Changes in health status measured by PGIS
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 have an effect on eGFR	Change in eGFR from baseline
To explore whether dapagliflozin compared to placebo improves KCCQ summary scores, subscores of TSS (Symptom frequency and symptom burden) and domains	Change in Clinical summary score, TSS sub-scores, Overall summary score, QoL score
To collect and store blood samples for future exploratory genetic research	Not applicable. Results will be reported separately

BP Blood pressure; CV Cardiovascular; EQ-5D-5L EuroQol five-dimensional five-level questionnaire
HF Heart failure; HFrEF Heart failure with reduced ejection fraction; KCCQ Kansas City Cardiomyopathy Questionnaire NYHA New York Heart Association

4. STUDY DESIGN

4.1 Overall design

This is an international, multicentre, parallel-group, event-driven, randomised, double-blind, placebo-controlled study in HFpEF patients, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background regional standard of care therapy, including treatments to control co-morbidities, in reducing the composite of CV death or heart failure events.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

Adult patients with HFpEF (defined for the purposes of this study as LVEF >40% and evidence of structural heart disease) aged ≥40 years and with NYHA class II-IV who meet the inclusion criteria, and none of the exclusion criteria, will be randomised in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo. Randomised treatment should be started as soon as possible and within 24 hours after randomisation. It is estimated that approximately 8000 patients at approximately 400-500 sites in 20-25 countries will be enrolled to reach the target of approximately 4700 randomised patients.

Study closure procedures will be initiated when the predetermined number of primary endpoints are predicted to have occurred (n=844), i.e. the Primary Analysis Censoring Date (PACD). Patients should be scheduled for a Study Closure Visit (SCV) within 6 weeks of the PACD. The anticipated total study duration is approximately 33 months dependent on randomisation rate and event rate. The study duration, and the number of patients, may be changed if the randomisation rate or the event rate is different than anticipated. The study may be terminated early if a clear harmful effect of the study treatment is detected during the DMC review, or due to DMC recommendations following pre-specified interim analyses (see Section 9.5).

Data on baseline characteristics, endpoints and AEs will be collected through a validated electronic data capture (EDC) system with electronic case report forms (eCRFs).

4.2 Scientific rationale for study design

This is a randomised, multi-centre, double-blind, parallel-group study. Randomisation and double-blinding will minimise potential bias. The target population includes adult (aged ≥ 40 years) male and female patients with HFpEF, which is defined in this study as individuals with an established diagnosis of heart failure and a LVEF >40% and structural heart disease who meet natriuretic peptide thresholds. The requirement of demonstrated structural heart disease (i.e. left ventricular

hypertrophy or left atrial enlargement[1]) and elevated natriuretic peptides aims to support the diagnosis of heart failure, since other common co-morbidities may cause overlapping symptoms. Most randomised patients will be out-patients. However, to address a specific need in a period with high risk for events, a proportion of patients will be enrolled and randomised during hospitalisation for heart failure or within 21 days of discharge from hospitalisation for heart failure (subacute subgroup).

The study population will include patients both with and without T2D, as the beneficial haemodynamic effects of dapagliflozin appear to be independent of the glycaemic effect, and can therefore be expected in both groups. Enrolment in the study may be capped based on the proportion of patients with/without T2D, in certain LVEF categories, in each NYHA class, with/without atrial fibrillation, randomised during or early after HF hospitalisation (subacute subgroup), and geographic region.

The control group will receive placebo; there are no approved pharmacological treatments for HFpEF that could be utilised as a comparator. All patients will be treated according to local guidelines on standard of care treatment for patients with HFpEF, focusing on treatment of HF symptoms (e.g. diuretics) and comorbidities (including treatment for high blood pressure, ischaemic heart disease, atrial fibrillation).

The study population will include patients with eGFR $\geq$ 25 ml/min/1.73m^2. Patients with reduced renal function have a clinical picture with increased intra-glomerular pressure, hypertension, proteinuria and fluid/sodium overload and SGLT2 inhibition can improve all these abnormalities through metabolic-independent mechanisms. Thus, patients with heart failure and reduced renal function could be expected to benefit from treatment with dapagliflozin.

The primary efficacy endpoints of the study are adjudicated CV death and HF events (hospitalisation for HF or urgent HF visit). The rationale for selecting CV death over all-cause death is the expectation that HF treatment will decrease CV death and not all potential causes of death (Zannad et al 2014). Heart failure events include both HF hospitalisations and unplanned HF visits requiring urgent treatment independently of whether the exacerbation of HF results in hospitalisation (according to CDISC definitions; Hicks et al 2014; Hicks et al. 2018 Hicks KA, Mahaffey KW, Mehran R, Nissen SE, et alCardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021–34 These are the same endpoint

[1] Left Atrial Enlargement defined by at least 1 of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm^2 or LA volume ≥55 mL or LA volume index ≥29 mL/m^2. Left Ventricular Hypertrophy defined by septal thickness or posterior wall thickness ≥1.1 cm

definitions currently employed in the Sponsor's ongoing HFrEF outcome study (Dapa-HF; Study D1699C00001).

The rationale for including outpatient 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. As stated in EMA Guidance 2016, '…patient are often managed for episodes of transient decompensation or worsening HF in outpatient settings (eg, emergency departments, observation units, other outpatient settings). The capture of events of worsening HF without hospitalisation may be warranted as an additional endpoint.' Including only hospital admissions is likely to overlook a modest but significant proportion of episodes of worsening HF (Skali et al 2014, Okumura et al 2016, Greene at al 2000).

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 the treatment effects on 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 (Greene at al 2000, Spertus et al 2005).

4.3 Justification for dose

The 10 mg dose of dapagliflozin has a well-characterised efficacy and safety profile in the T2D clinical development program and is the recommended dose in the majority of countries worldwide.

From a pharmacokinetic perspective, the currently approved dapagliflozin dose of 10 mg once daily is appropriate for use in patients with HFpEF. Slightly higher systemic exposure to dapagliflozin is expected in HFpEF patients when symptomatic, based on the dual renal and hepatic metabolism of dapagliflozin and the lower perfusion of these organs in this patient group. However, the increase in systemic exposure of 10 mg dapagliflozin is not anticipated to warrant dose adjustment in HF patients. Moreover, the anticipated slightly higher systemic exposure to dapagliflozin is likely to be beneficial in HF patients, by compensating for the reduced renal perfusion and consequently lower renal glucose and sodium filtered loads in these patients. Doses lower than 10 mg are therefore unlikely to provide as much benefit to patients with HF as the 10-mg dose. Lastly, no changes in dose of concomitant medications in the HFpEF population are needed due to a lack of clinically meaningful drug-drug interactions for dapagliflozin with current medications used for treatment of patients with HFpEF, including standard of care medications used to control co-morbidities in this patient group.

In the dapagliflozin clinical program, there are no dose-related SAEs that preclude the use of 10 mg as a preferred dose. Additionally, in a post-hoc analysis of data from 320 patients with a documented history of HF and concomitant T2D in placebo-controlled clinical trials, dapagliflozin 10 mg was found to be well tolerated in this population (Kosiborod et al 2017b).

There are mechanistic reasons for choosing the 10-mg dose as well. One hypothesis of underlying pathophysiology in HFpEF is abnormal pressure coupling between the left ventricle and aorta, and drugs that reduce aortic stiffness may have beneficial effects in patients with HFpEF (Borlaug and

Paulus 2011). Studies examining the highest approved dose for empagliflozin have reported improvements in aortic elasticity (Chilton et al 2015,Cherney et al 2014); similar studies are ongoing with dapagliflozin. In a completed placebo-controlled study, treatment with dapagliflozin 10 mg resulted in improvements in parameters associated with arterial remodelling in addition to lowering blood pressure in patients with T2D (Ott et al 2017). This prior work suggests that selecting the 10-mg dose of dapagliflozin is reasonable from a mechanistic perspective to demonstrate a clinical effect.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

The study may be terminated at individual study sites if the study procedures are not being performed according to GCP, or if no patients are recruited. Patients from terminated sites will have the opportunity to be transferred to another site to continue the study. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin, or due to recommendation by the DMC. Regardless of the reason for termination, all data required by the protocol at the time of discontinuation of follow-up will be collected. In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

In this protocol, 'enrolled' patients are defined as those who sign the informed consent form (ICF) and received E-Code. The ICF process is described in Appendix A 3. 'Randomised' patients are defined as those who undergo randomisation and receive a randomisation code.

Patients are eligible to be randomised in the study only if all of the following inclusion criteria and none of the exclusion criteria apply. Enrolled patients who for any reason are not randomised are considered screen failures (see Section 5.4).

5.1 Inclusion criteria

Subjects are eligible to be randomised in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

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

2. Male or female patients age ≥40 years.

3. Documented diagnosis of symptomatic heart failure (NYHA class II-IV) at enrolment, and a medical history of typical symptoms/signs[2] of heart failure ≥6 weeks before enrolment with at least intermittent need for diuretic treatment.

4. Left Ventricular Ejection Fraction (LVEF) >40% and evidence of structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement[3]) documented by the most recent echocardiogram, and/or cardiac MR within the last 12 months prior to enrolment. For patients with prior acute cardiac events or procedures that may reduce LVEF, e.g. as defined in exclusion criterion 6, qualifying cardiac imaging assessment at least 12 weeks following the procedure/event is required.

5. NT-pro BNP ≥300 pg/ml at Visit 1 for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at Visit 1, NT-pro BNP must be ≥600 pg/mL.

6. Patients may be ambulatory, or hospitalized; patients must be off intravenous heart failure therapy (including diuretics) for at least 12 hours prior to enrolment and 24 hours prior to randomisation.

5.2 Exclusion criteria

1. Receiving therapy with an SGLT2 inhibitor within 4 weeks prior to randomisation or previous intolerance to an SGLT2 inhibitor

2. Type 1 diabetes mellitus (T1D)

3. eGFR <25 mL/min/1.73 m^2 (CKD-EPI formula) at Visit 1

[2] Typical symptoms associated with heart failure: breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, ankle swelling;
Signs associated with Heart Failure:
More specific: elevated jugular venous pressure, hepatojugular reflex, third heart sound (gallop rhythm), laterally displaced apical impulse
Less specific: weight gain (>2 kg/week), weight loss (in advanced HF), tissue wasting (cachexia), cardiac murmur, peripheral oedema (ankle, sacral, scrotal), pulmonary crepitations, reduced air entry and dullness to percussion at lung bases (pleural effusion), tachycardia, irregular pulse, tachypnoea, cheyne stokes respiration, hepatomegaly, ascites, cold extremities, oliguria, narrow pulse pressure

[3] Left Atrial Enlargement defined by at least 1 of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm^2 or LA volume ≥55 mL or LA volume index ≥29 mL/m^2. Left Ventricular Hypertrophy defined by septal thickness or posterior wall thickness ≥1.1 cm

4. Systolic blood pressure (BP) <95 mmHg on 2 consecutive measurements at 5-minute intervals, at Visit 1 or at Visit 2

5. Systolic BP≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments, on 2 consecutive measurements at 5-minute intervals, at Visit 1 or at Visit 2.

6. MI, unstable angina, coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), ablation of atrial flutter/fibrillation, valve repair/replacement within 12 weeks prior to enrolment. Before enrolment, these patients must have their qualifying echocardiography and/or cardiac MRI examination at least 12 weeks after the event.

7. Planned coronary revascularization, ablation of atrial flutter/fibrillation and valve repair/replacement.

8. Stroke or transient ischemic attack (TIA) within 12 weeks prior to enrolment

9. Probable alternative or concomitant diagnoses which in the opinion of the investigator could account for the patient's HF symptoms and signs (e.g. anaemia, hypothyroidism)

10. Body mass index >50 kg/m^2

11. Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalisation for exacerbation of COPD requiring ventilatory assist within 12 months prior to enrolment)

12. Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronisation therapy.

13. HF due to any of the following: known infiltrative cardiomyopathy (e.g. amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), or uncorrected primary valvular disease

14. A life expectancy of less than 2 years due to any non-cardiovascular condition, based on investigator's clinical judgement.

15. 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

16. Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin).

17. Acute or chronic liver disease with severe impairment of liver function (e.g., ascites, oesophageal varices, coagulopathy)

18. Women of child-bearing potential (i.e. those who are not chemically or surgically sterilised or post-menopausal) not willing to use a medically accepted method of contraception considered reliable in the judgment of the investigator OR who have a positive pregnancy test at randomisation OR who are breast-feeding

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

20. Previous randomisation in the present study

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

5.3 Lifestyle restrictions (not applicable)

5.4 Screen failures

Enrolled patients who are found not eligible (i.e. not meeting all the inclusion criteria or fulfilling any of the exclusion criteria) must not be randomised or initiated on treatment.

Screen failures are defined as patients who signed the informed consent form to participate in the study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria (reason for screen failure), and any serious adverse event (SAE).

Screen failures may be re-enrolled one time during the study if the Investigator considers that the patient may be eligible for participation in this study at another time point. Re-enrolled patients should be assigned the same enrolment code as for the initial enrolment. All enrolment assessments and procedures, including signing the informed consent form, should be performed again.

5.5 Procedures for handling of randomized not eligible patients

If a patient is randomised and later found not eligible, the Investigator should immediately inform the AstraZeneca representative, who will report the protocol deviation to the AstraZeneca Study Physician.

Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. Regardless of whether study treatment is discontinued or not, the patient should continue his/her participation in the study for follow-up of endpoints and other protocol-defined study procedures until the end of the study. Consistent with the intention-to-treat principle, all randomised patients are included in the efficacy analysis according to randomised treatment assignment. The AstraZeneca Study Physician must ensure that the protocol deviation and the rationale for the decision to discontinue or continue study treatment are appropriately documented.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to dapagliflozin or matching placebo.

6.1 Treatments administered

Table 4 Study Treatments

	Dapagliflozin	Placebo
Investigational Product name	Dapagliflozin 10 mg	Matching placebo 10 mg
Dosage formulation	Green, diamond shaped, film coated tablets 10 mg	Green, diamond shaped, film coated tablets placebo
Route of administration	Oral	Oral
Dosing instructions	Once daily	Once daily
Packaging and labelling	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements
Provider	AstraZeneca	AstraZeneca

The tablets contain lactose, in quantities not likely to cause discomfort in lactose-intolerant individuals.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

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

Only patients randomised in the study may receive IP and only authorised site staff may supply or administer IP. The administration of all investigational products should be recorded in the appropriate sections of the eCRF.

The Investigator is responsible for IP accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

The investigator will retain the returned IP until the AZ representative or delegate collects it, along with any IP 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 IP is destroyed. The AZ representative or delegate will advise on the appropriate method for destruction of unused IP.

6.3 Measures to minimise bias: randomisation and blinding

All patients will be centrally assigned to randomised IP using an interactive voice/web response system (IxRS). Randomisation to IP will be performed in balanced blocks to ensure approximate balance between the treatment groups (1:1). The randomisation codes will be computer generated and loaded into the IxRS database. Before the study is initiated, the telephone number and call-in directions for the IxRS and/or the log-in information and directions for the IxRS will be provided to each site.

If a randomised patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn randomised patients will be included in the intention to treat analysis.

The IxRS will provide the Investigator with the kit identification number to be allocated to the patient at each dispensing visit. At all visits where IP is dispensed, site personnel will do a kit verification in IxRS before providing the IP bottle to the patient. Routines for this will be described in the IxRS user manual that will be provided to each centre.

The blinding of treatment is ensured by using a double-blind technique. 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 randomisation code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator is to document and report the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff.

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. Randomisation 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.

6.3.1 Stratification and capping

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

6.3.1.1 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. Stratification on T2D at the time of randomisation is based on:

- Established diagnosis of T2D

OR

- HbA1c ≥6.5% (48 mmol/mol) shown at central laboratory test at enrolment (Visit 1)

6.3.1.2 Capping

The intent is to enrol a typical cross-section of patients with HFpEF 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, subacute subgroup (i.e. randomised in-hospital or within 21 days from discharge) and atrial fibrillation status at Visit 1 may be capped in IxRS to avoid over- or under-representation of these patient subgroups.

6.4 Treatment compliance

The administration of all IP should be recorded in the appropriate sections of the eCRF. Any change from the dosing schedule should be recorded in the eCRF.

Patients will be asked to return all unused IP and empty packages to the clinic at the site visit except Visit 3. At each visit, any patient found to be non-compliant will be counselled on the importance of taking their IP as prescribed. The investigator or delegate will enter the number of returned tablets in the eCRF.

The Investigational Product Storage Manager is responsible for managing IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.5 Concomitant therapy

All patients should be treated according to regional standard of care of HFpEF and existing comorbidities (including treatment of hypertension, ischemic heart disease, atrial fibrillation, diabetes, hyperlipidaemia). Background medications should be part of clinical practice and will not be provided by the Sponsor.

6.5.1 Prohibited medication

Concomitant treatment (i.e., treatment in combination with IP) with open label SGLT2 inhibitors e.g., dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and

fix dose combinations containing these drugs should not be used. 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. If treatment with an SGLT2 inhibitor alone or in combination is deemed essential, IP must be discontinued before that treatment is started.

6.5.2 Recording of concomitant treatment

Recording of relevant concomitant medications in eCRF will be made according to the schedule of activities (Table 1). These include medications for cardiovascular conditions as well as diabetes mellitus.

6.5.3 Heart failure background standard of care

The patients should be on background standard of care therapies for patients with HFpEF according to local guidelines, including diuretics when needed to control symptoms and volume overload and adequate treatment of co-morbidities such as hypertension and ischaemic heart disease.

6.5.4 Anti-diabetes treatment

6.5.4.1 Background

More than 40% of patients with established HF are estimated to have T2D (Kristensen et al 2016). Therefore, it is expected that a large proportion of patients will have an established T2D diagnosis when included in this study and that some patients will develop T2D during the course of the study. Treatment of diabetes should follow established guidelines, such as 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).

6.5.4.2 Treatment of patients with established diagnosis of type 2 diabetes

Diabetes medications at baseline and during the study will be recorded in the eCRF. Patients with T2D at randomisation will continue their T2D treatment. SGLT2-inhibitors should be avoided (see Section 6.5.1). Patients treated with insulin or insulin secretagogues have a higher risk of experiencing hypoglycaemic events compared with those treated with other antidiabetic agents. If needed, T2D treatments may be adjusted at the discretion of the Investigator or diabetes health care provider.

6.5.5 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

6.6 Dose modification (not applicable)

6.7 Treatment after the end of the study

The patients will stop taking IP at the study closure visit (SCV). Remaining IP will be collected at that time. Post-study treatment will not be provided by the Sponsor. Patients should receive standard of care therapy after the SCV, at the discretion of the Investigator.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Discontinuation from study treatment is NOT the same thing as a withdrawal from the study. If the patient temporarily or permanently discontinues IP, the patient should remain in the study and it is important that the scheduled study visits and data collection continue according to the study protocol until study closure.

- Patients may be discontinued from IP in the following situations:
- Contraindication to further dosing with IP, in the opinion of the Investigator, such as Adverse event or other safety reasons.
- Severe non-compliance with the study protocol.
- Diabetic ketoacidosis (DKA). Consider temporarily interrupting IP if DKA is suspected. If DKA is confirmed, IP should be discontinued permanently.
- Positive pregnancy test (discontinue IP and notify Sponsor representative).
- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.

See the Table 1 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation

Every attempt should be made to maintain patients on IP during the course of the study. If IP has been interrupted, it should be re-introduced as soon as, in the opinion of the Investigator, the patient's condition is stable.

7.1.1.1 Unexpected acute declines in eGFR

If an unexpected, acute decline in kidney function is observed, the patient should be evaluated and temporary interruption of IP should be considered. 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.

7.1.1.2 Volume depletion/hypotension

Patients with clinically relevant symptoms/signs of suspected volume depletion and/or hypotension, should in addition to considering temporary interruption of IP have their regular medication reviewed, and consideration given to reducing the dose of, or stopping concomitant

medications, as assessed on an individual basis, including diuretics and drugs that lower blood pressure. The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in light of the patient's symptoms and signs.

7.1.1.3 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.

7.1.2 Procedures for discontinuation of study treatment

Investigators should instruct their patients to contact the site before or at the time IP is stopped. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. Generally, AEs, SAEs, and potential endpoint events should not lead to IP discontinuation, unless there is a clear clinical rationale to do so.

The date of last intake of IP should be documented in the eCRF. All IP should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing IP should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of IP, for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn from the study.

Restart of randomised IP is always encouraged. 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.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and it is not possible for the site to get contact with the patient. To optimise the chance of getting in contact with the patient during the study, Investigators should record as much contact information as possible at the start of the study including home phone, mobile phone, holiday home phone, family member phone numbers, email address, and social media contact details.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.

- Before a patient is deemed potentially lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by, e.g. repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.

- Efforts to reach the patient should continue until the end of the study. Information regarding vital status should always be collected if possible.

7.3 Withdrawal from the study

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 has received appropriate information about and does not agree to any kind of further assessments or contact, including modified follow up options (see Section 7.1.2). 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 from the study 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. If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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, in compliance with local privacy laws/practices.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (see Section 1.1).

An Electronic Data Capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g. LVEF assessment) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1 Enrolment Period

8.1.1 Visit 1, Enrolment (Day -21 to Day -1)

Enrolment of hospitalized patients is allowed.

At enrolment the following assessments and procedures will be completed:

- The patient signs the ICF
  - Patients who agree to the optional sampling of blood for genetic research will provide their consent
- The investigator reviews the inclusion and exclusion criteria
- The patient will be enrolled and assigned an E-code in IxRS assuming inclusion/exclusion criteria are met
- Demography and relevant medical history (including prior cardiac imaging assessments) will be recorded
- A physical examination will be conducted
- NYHA Functional Classification will be evaluated and recorded
- 12-lead ECG will be recorded
- Vital signs (BP, pulse), height and weight will be assessed and recorded
- Blood samples will be taken for NT-proBNP, creatinine (for calculation of eGFR) and HbA1c assessment (central laboratory)

8.2 Treatment period

8.2.1 Visit 2, Randomisation (Day 1)

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

Randomisation of hospitalized patients is allowed.

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

- Medical history (including cardiac imaging assessments) will be re-assessed
- A physical examination will be conducted
- A pregnancy test for women of child-bearing potential will be done locally with a dipstick provided by central laboratory with result recorded in the medical record
- Vital signs (BP, pulse) will be assessed and recorded
- NYHA Functional Classification will be evaluated and recorded
- The investigator will re-assess the inclusion and exclusion criteria
- KCCQ, PGIS and EQ-5D-5L questionnaires will be completed
- Review of concomitant medication and recording of relevant medications
- If the patient has experienced any SAEs since last visit, this will be recorded in the eCRF
- Randomisation 1:1 ratio to IP (either dapagliflozin at 10 mg or placebo) will be done in IxRS
- 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
- Patients who have consented to sampling for genetic research, will provide a blood sample

8.2.2 Visit 3 (Day 30; ±7 days):

At Visit 3, the following assessments and procedures will be conducted:

- KCCQ and PGIS questionnaires will be completed
- NYHA Functional Classification will be evaluated and recorded

- Vital signs (BP, pulse) will be assessed and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events.
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF
- Blood samples will be taken for creatinine (for calculation of eGFR) assessment (central laboratory)

8.2.3 Visit 4 (Day 120 ±7 days):

At Visit 4, the following assessments and procedures will be conducted:

- KCCQ and PGIS questionnaires will be completed
- NYHA Functional Classification will be evaluated and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events.
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.
- Blood samples will be taken for creatinine (for calculation of eGFR) assessment (central laboratory)
- IP will be dispensed via IxRS to the patient. Drug accountability of the returned IP will be checked. The patient will be instructed to take the IP in accordance with protocol and without interruptions

8.2.4 Visit 5 (Day 240 ±7 days)

At Visit 5, the following assessments and procedures will be conducted:

- KCCQ, PGIS and EQ-5D-5L questionnaires will be completed
- NYHA Functional Classification will be evaluated and recorded
- Review and updating of concomitant medication and recording of relevant medications

- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.
- IP will be dispensed via IxRS to the patient. Drug accountability of the returned IP will be checked. The patient will be instructed to take the IP in accordance with protocol and without interruptions.

8.2.5 Visit 6 (Day 360 ±7 days)

At Visit 6, the following assessments and procedures will be conducted:

- Vital signs (BP, pulse), and weight will be assessed and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events.
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.
- IP will be dispensed via IxRS to the patient. Drug accountability of the returned IP will be checked. The patient will be instructed to take the IP in accordance with protocol and without interruptions.
- Blood samples will be taken for creatinine (for calculation of eGFR) assessment (central laboratory)

8.2.6 Visit 7 and onwards (Day 480 and every 120 days ±14 days)

At visit 7 and subsequent visits, the following assessments and procedures will be conducted:

- Vital signs (BP, pulse), and weight will be assessed and recorded every 12 months
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events.

- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.

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

- Blood samples will be taken for creatinine (for calculation of eGFR) assessment (central laboratory) every 12 months

8.2.7 Premature Treatment Discontinuation Visit

Patients who prematurely and permanently discontinue treatment with IP should return for a premature treatment discontinuation visit (PTDV), which will be done as soon as possible after last dose of IP. The following assessments and procedures will be conducted:

- KCCQ, PGIS and EQ-5D-5L questionnaire will be completed

- NYHA Functional Classification will be evaluated

- Vital signs (BP, pulse) and weight will be assessed and recorded

- Review and updating of concomitant medication and recording of relevant medications

- Review and recording of any cardiac and HF related procedures

- Review of potential efficacy and safety events

- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF

- Drug accountability of the returned IP will be checked

Patients who discontinue treatment prematurely should attend all study visits according to plan, including the study closure visit (SCV). Patients may re-start treatments if assessed as appropriate by the Investigator. For further details regarding discontinuations from IP, please see Section 7.1.

8.2.8 Study Closure Visit

A primary analysis censoring date (PACD) will be declared based on the rate of accrued endpoints. A study closure visit (SCV) will be scheduled within 6 weeks of the PACD. All patients (including any patients who have discontinued treatment with IP) should return for this visit.

The patient will stop taking IP at the SCV. Remaining IP will be collected at that time and drug accountability will be checked. The following assessments and procedures will be conducted:

- KCCQ, PGIS and EQ-5D-5L questionnaire will be completed
- NYHA Functional Classification will be evaluated
- A physical examination will be conducted
- Vital signs (BP, pulse) and weight will be assessed and recorded.
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF
- Drug accountability of the returned IP will be checked

8.2.9 Unscheduled visits

An unscheduled on-site or telephone visit may occur in-between scheduled on-site visits (for example assessment of potential endpoint events or safety events).

8.3 Efficacy assessments

8.3.1 Efficacy event capture

Efficacy events (i.e. death, hospitalisation or urgent visits for HF) will be collected by site personnel according to the study visit schedule. All potential efficacy events should be recorded as an AE and on additional event modules in the eCRF. If the potential efficacy event fulfils SAE criteria (see Appendix B 2) the site is to record and report these events to the sponsor or designee within timelines described in Section 8.6.

NYHA classification will be done by the Investigators and recorded in the eCRF. PROs will be collected for all patients throughout the study period via a hand-held electronic device. All-cause hospitalisations will be derived from SAE reports.

8.3.2 Efficacy event adjudication

A Clinical Events Adjudication (CEA) Committee will be established for this trial and adjudicate primary efficacy events in accordance with adjudication criteria detailed in the CEA charter.

Events to be adjudicated include components of the primary efficacy endpoint: deaths, hospitalisation for HF, and urgent HF visits. All deaths will be adjudicated to determine if they are CV or non-CV deaths. All adjudication will be done on an ongoing basis throughout the trial.

8.3.3 Clinical Outcome Assessments (COA)

A COA is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. Patient Reported Outcomes (PROs) is one of the types of COAs. A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of anyone else. PROs have become a significant endpoint when evaluating benefit/risk of treatments in clinical trials. The following PROs will be collected: KCCQ, PGIS and EQ-5D-5L (see Appendix J, Appendix L, Appendix M).
PROs will be collected for all patients throughout the study period via a hand-held electronic device. See study of assessment (See Table 1) for the timing of collection. The ePRO devices should be administered prior to first dose at visit 2/randomisation. Site staff should stress that the information is confidential.

8.3.3.1 KCCQ

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item, self-administered disease specific instrument and has shown to be a valid, reliable and responsive measure for patients with HF (Greene at al 2000, Spertus et al 2005). The KCCQ was developed to independently measure the patient's perception of their health status, which includes heart failure-related symptoms (frequency, severity and recent change), impact on physical and social function, self-efficacy and knowledge, and how their heart failure impacts their quality of life (QOL). Scores are transformed to a range of 0-100. Higher scores represent a better outcome.

The KCCQ tool quantifies the following six (6) distinct domains and two (2) summary scores:

- KCCQ Symptom Domain quantifies the frequency and burden of clinical symptoms in heart failure, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea and patients' edema/swelling. An overall symptom score is generally used in analyses; subscale scores for both frequency and severity are also available. The total symptom Score incorporates the symptom domains into a single score

- KCCQ Physical Function Domain measures the limitations patients experience, due to their heart failure symptoms, in performing routine activities. Activities are common, gender-neutral, and generalizable across cultures, while also capturing a range of exertional requirements

- KCCQ Quality of Life Domain is designed to reflect patients' assessment of their quality of life, given the current status of their heart failure

- KCCQ Social Limitation Domain quantifies the extent to which heart failure symptoms impair patients' ability to interact in a number of gender-neutral social activities

- KCCQ Self-efficacy Domain quantifies patients' perceptions of how to prevent heart failure exacerbations and manage complications when they arise. This scale is not included in the summary scores

- KCCQ Symptom Stability Domain measures recent changes in patients' symptoms; their shortness of breath, fatigue or swelling. It compares patients frequency of heart failure symptoms at the time of completing the KCCQ with their frequency 2 weeks ago. As a measure of change, it is most interpretable as a baseline assessment of the stability of patients' symptoms at the start of a study and shortly thereafter, as a measure of the acute response to treatment. This domain is not included in the summary scores.

- Clinical Summary Score includes total symptom and physical function scores to correspond with NYHA Classification

- Overall Summary Score includes the total symptom, physical function, social limitations and quality of life scores

8.3.3.2 Patient Global Impression of Severity (PGIS)

The PGIS item is included to assess how a patient perceives his/her overall current severity of heart failure symptoms. Patients will choose from response options from "no symptoms" to "very severe"

8.3.3.3 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.

8.3.3.4 Administration of electronic PROs

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. A key aspect of study success is to have high PRO compliance. Therefore, it is essential to follow SoA and that sites make sure the device is charged and fully functional at all times in order to minimize missing data.

It is important that the site staff explains the value and relevance of PRO data: to hear directly from patients how they feel. The following best practice guidelines should be followed:

- 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 (except the Visit 2: eligibility confirmation before the KCCQ)

- Before being seen by the investigator

- PRO questionnaires must be completed by the patient in private

- The appointed site personnel should also stress that the information is confidential. Therefore, if the patient has any medical problems, he or she should discuss them with the doctor or research nurse separately from the ePRO assessment

- 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.

8.4 Safety assessment

Planned time points for all safety assessments are provided in the schedule of activities (Table 1).

8.4.1 Physical examinations

A 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.

The assessment dates will be recorded in the eCRF.

8.4.2 Vital Signs

- Pulse and BP will be measured twice at all applicable visits, and all measurements will be recorded in the eCRF.

- The measurements should be done before any blood sampling. The measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- The measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

8.4.3 Electrocardiogram

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 baseline (Visit 1) after the patient has been lying down to rest for at least 5 minutes, to confirm presence or absence of atrial fibrillation/flutter at enrolment. t rhythm will be reported in the eCRF. The baseline ECG should be stored and be made available upon request for adjudication purposes.

8.4.4 Safety laboratory assessments

Serum creatinine will be collected for calculation of eGFR using CKD-EPI equation (Levey at al 2009).

8.4.5 Other safety assessments (not applicable)

8.4.6 Other clinical assessments

8.4.6.1 Body weight and height

The patient's body weight will be measured with light clothing and no shoes. If the patient has a prosthetic limb, this should be consistently 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.

8.5 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of a SAEs and DAEs, amputation and events potentially placing the patient at risk for a lower limb amputation (preceding events). For information on how to follow-up AEs see Section 8.5.3.

8.5.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting SAEs or DAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

Safety information on SAEs and DAEs, amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs will be collected and entered into eCRFs by site personnel according to the study visit schedule.

If the potential efficacy event fulfils SAE criteria (see Appendix B 2) the site is to record and report these events to the Sponsor or designee within timelines described in Section 8.6.1.

8.5.1.1 Adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs ("preceding events")

To ensure that data on amputations is systematically collected, amputations and underlying conditions relevant to amputation 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 to amputation, non-serious and serious events potentially placing the patient at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as AE/SAE whether or not an amputation has taken place. The lower limb amputation "preceding events" of interest include diabetic foot related conditions, vascular, volume depletion, wounds/injury/trauma, infection and neuropathy. If any of these or other potentially relevant events have occurred, relevant information must be provided (this will be collected on a dedicated eCRF page - for details see eCRF instruction)".

8.5.1.2 Capture of DKA events

For SAEs or DAEs reported by the Investigator as Diabetic Ketoacidosis (DKA - see definition below) additional information will be recorded on specific eCRF pages in addition to the AE/SAE form.

8.5.1.3 DKA definition

A diagnosis of Diabetic Ketoacidosis should only be made in a clinical setting consistent with DKA (based on patient history, symptoms, and physical exam) and in the absence of more likely alternative diagnoses and causes of acidosis (such as lactic acidosis). The following biochemical data should support diagnosis:

- Ketonaemia ≥3.0 mmol/L and/or significant ketonuria (more than 2+ on standard urine sticks)
- At least one of the following criteria suggesting high anion gap metabolic acidosis:
  - Arterial or Venous pH ≤7.3
  - Serum bicarbonate ≤18 mEq/L
  - Anion gap [Na – (Cl + HCO3)] >10

8.5.1.4 Capture of cardiac ischaemic events and stroke

For myocardial infarctions, unstable angina and stroke additional information will be recorded on specific eCRF pages in addition to the AE/SAE form.

The diagnosis of stroke, MI and unstable angina should be made according to standard clinical practice and align with the definition for stroke in the standardised definitions for endpoints (Hicks et al. 2018
Hicks KA, Mahaffey KW, Mehran R, Nissen SE, et alCardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021–34) described in Appendix C.

8.5.1.5 Capture of additional laboratory values

Any additional safety laboratory assessments during the study period, including creatinine, will be obtained per the Investigator's medical judgment in the course of standard care using local laboratories. Laboratory values would be recorded only on SAE eCRFs as part of narrative information, per the Investigator's judgment.

8.5.2 Time period and frequency for collecting AE and SAE information

Non- serious adverse events as defined per protocol will be collected from randomisation (Visit 2), throughout the treatment period until and including the patient's last visit (the study closure

visit). Serious adverse events are recorded from the time of signing of informed consent form throughout the treatment period until and including the patient's last visit.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix BAppendix B.

8.5.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAE and events of amputation and potential preceding events will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

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.

8.5.4 Adverse event data collection

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 Investigational Product(s) (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

8.5.5 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 B to the Clinical Study Protocol.

8.5.6 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 they fulfil the criteria specified in Section 8.5.2. 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.

8.5.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated vital signs and laboratory values will be summarised in the clinical study report. Deterioration as compared with baseline in protocol-mandated 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 IP. If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment of IP, and the associated vital sign will be considered as additional information.

8.5.8 Disease-under study (DUS) (not applicable)

8.5.9 Disease progression (not applicable)

8.6 Safety reporting and medical management

8.6.1 Reporting of serious adverse events

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 adverse events 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 EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.6.1.1 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 8.6.1).

In addition, fatal AEs and potential HF endpoints will be centrally adjudicated by an independent CEA committee (see Section 8.3.1 and 8.3.2). 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 8.6.1) 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).

8.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study patient has received any IP. If a pregnancy is reported, the Investigator should inform the sponsor within 24 hours of learning of the pregnancy. Abnormal

pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.6.2.1 Maternal exposure

Women of childbearing potential who are not using contraception as defined in Section 5.2; exclusion criterion number 18 are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

Dapagliflozin must not be used in the second and third trimesters of pregnancy. In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

There are no adequate and well-controlled studies of dapagliflozin in pregnant women. When pregnancy is detected, investigational product(s) should be discontinued.

8.6.3 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 without associated symptoms is only recorded on the Overdose eCRF module

- 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

If an overdose on an AstraZeneca IP 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 8.5.2. For other overdoses, reporting must occur within 30 days.

8.7 Pharmacokinetics (not applicable)

8.8 Pharmacodynamics (not applicable)

8.9 Optional exploratory genetics

Approximately 6 mL blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D.

8.10 Biomarkers (not applicable)

8.11 Health Economics (not applicable)

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

For the primary and secondary endpoints, the following hypothesis will be tested at the 4.980 % 2-sided level:

H0: HR [dapagliflozin:placebo] =1

versus

H1: HR [dapagliflozin:placebo] ≠1

9.2 Sample size determination

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo added to standard of care in reducing the composite of CV death and heart failure events (hospitalisation for HF or urgent HF visit). Assuming a true hazard ratio (HR) of 0.80 between dapagliflozin and placebo, using a two-sided alpha of 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 HR was chosen as a conservative assumption based on the observed HR 0.72 (95% confidence interval 0.50-1.04) for the composite of HF hospitalisation and CV death in patients with HF at baseline in the EMPA-REG OUTCOME trial (Fitchett et al 2016) and HR 0.61 (0.46-0.80) for patients with history of HF in the CANVAS program (Rådholm et al 2018) considering that these were post-hoc analyses in subgroups with limited documentation of baseline HF diagnosis, not characterised by ejection fraction.

The event rate assumptions are based on sub analyses of the TOPCAT and I-PRESERVE studies by geographic region, NT-proBNP levels, prior hospitalisation for HF, and T2D status (Pfeffer et al 2015, Kristensen et al 2015 Kristensen et al 2017). The sample size calculation builds on the assumption of an annual event rate of 9% in the placebo group for the majority of prevalent HFpEF patients, importantly all with NT-proBNP ≥300 pg/ml by inclusion criterion. Additionally, a subgroup of patients due to be discharged or recently discharged from a HF hospitalisation (here

denoted 'subacute' patients) with a higher event rate is planned to be included. Assuming 20% of patients from the sub-acute category with an annual event rate of 24% during the first year and 9% thereafter for the remainder of the study, (corresponding to an annualised rate of approximately 17% for sub-acute patients), approximately 4700 patients are estimated to provide the required number of 844 patients with a primary event during an anticipated recruitment period of 18 months and a minimal follow-up period of 15 months (total study duration 33 months, average follow-up 24 months). The study is event driven and the number of patients or duration may change if the event rate is lower than anticipated.

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.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Table 5 Population for analysis

Population	Description
Enrolled	All patients who sign the ICF
Full Analysis Set (FAS)	All patients who have been randomised to study treatment, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised investigational product assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the intention to treat analysis of primary and secondary variables.
Safety analysis set	All patients randomly assigned to Study treatment and who take at least 1 dose of investigational product. 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

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be developed prior to first patient randomised and any subsequent amendments will be documented, with final amendments finalised before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

9.4.1 Efficacy analyses

9.4.1.1 Analysis of the primary variable

The primary variable is the time from randomisation to first event included in the primary composite endpoint. The primary analysis will be based on the ITT principle using the FAS, including events occurring on or prior to the PACD, adjudicated by the CEA committee.

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. 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 analyse the time from randomisation to the first occurrence of each component of the primary composite endpoint. 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.

9.4.1.2 Analysis of the secondary variables

The 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. The rate ratio and its 95% confidence interval and corresponding two-sided p-value will be presented.

The proportion of patients with worsening NYHA classification from baseline to 8 months will be analysed by a logistic regression with treatment group, baseline NYHA and T2D at randomisation as factors. The odds ratio between treatment groups, its 95% confidence interval and corresponding two-sided p-value will be presented.

The analysis of change from baseline for KCCQ total symptom score at 8 months will be further detailed in the statistical analysis plan, e.g. with consideration of handling of patients who die. In addition to the secondary endpoint, total symptom score, the overall summary score, clinical summary score and domain scores will be analysed. A responder analysis will also be performed (more details presented in the SAP).

The analysis of time from randomisation to all-cause mortality will be analysed in the similar manner as the primary variable.

9.4.1.3 Subgroup analysis

Subgroup variables for the primary efficacy endpoint include demography, baseline disease characteristics, baseline concomitant medications and others. Cox proportional hazard model stratified for T2D with factors for treatment group, the subgroup variable and the interaction between treatment and subgroup will be used to examine treatment effects within relevant subgroups separately. A test of interaction between randomised treatment group and the subgroup

variable will be performed in each Cox model. 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.

9.4.1.4 Sensitivity analysis

Details of the sensitivity analysis for the primary and secondary endpoints will be provided in the SAP.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety analysis set. The number and percent of patients with SAEs, DAEs, amputations, and potential preceding events for lower limb amputations will be summarised by treatment group, and by system organ class and preferred term.

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

9.4.3 Methods for multiplicity control

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilised. The Type I error will be controlled at an overall two-sided 5% level for multiplicity across primary and secondary endpoints and in consideration of the planned interim analysis. With one interim analysis at 67%of events (see Section 9.5) the two-sided significance level in final analysis, α, will be 4.980%. Statistical significance will be assessed in the pre-specified order of the endpoints as specified in Section 3. If the primary endpoint is significant at level α, then the first secondary endpoint, recurrent HF hospitalisations and CV Death, will be tested at level α. If the first secondary endpoint is significant, then the α will be split between KCCQ total symptom score and NYHA class. If one of them is significant at level α/2, then the other can be tested at level α. If both KCCQ and NYHA class reach statistical significance, then all-cause mortality will be tested at significance level α.

9.5 Interim analyses

An interim analysis is planned to be performed including approximately 67% of the target number of patients with adjudicated primary endpoint events. There will in principle be one planned interim analysis for efficacy, with the possibility of the DMC to conduct 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 of interim analyses. The interim analysis will assess superiority of dapagliflozin to placebo. The interim analysis will have a nominal two-sided alpha level of 0.2%. At the interim analysis, the primary composite endpoint will be tested first 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 two-sided level of 0.2%. 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.

A futility analysis is planned to be performed at the same time as the planned interim analysis. The study may be stopped for futility if the observed HR is > 0.946, corresponding to a predictive power of 5%. If the futility criterion of the primary endpoint is met, then DMC will evaluate the totality of data, including potential benefits on patient reported outcomes to consider recommending ending the study for futility.

9.5.1 Data monitoring committee (DMC)

An independent data monitoring committee (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. 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 charter will be prepared to detail precise roles and responsibilities and procedures of the DMC.

10. REFERENCES

Ambrosy et al 2014
Ambrosy AP, Gheorghiade M, Chioncel O, Mentz RJ, Butler J. Global perspectives in hospitalised heart failure: regional and ethnic variation in patient characteristics, management, and outcomes. Curr Heart Fail Rep 2014 Dec;11(4):416-27.

Borlaug and Paulus 2011
Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 2011;32:670-9.

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

Butler et al 2014
Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC Heart Fail 2014 Apr;2(2):97-112.

Cherney et al 2014
Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, et al. The effect of the empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014;13:28.

Chilton et al 2015
Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metabo 2015;17:1180-93.

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 Feb 15;171(3):368-76.

EMA Guidance 2016
EMA 2016; Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (draft), Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/392958/2015.

FDA Draft Guidance for Industry 2016
Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices. Draft Guidance for Industry and Food and Drug Administration Staff. 16 September 2016.

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;14;37(19):1526-34.

Greene at al 2000
Greene SJ, Mentz RJ, Felker GM. Outpatient Worsening Heart Failure as a Target for Therapy: A Review. JAMA Cardiol. 2018 Jan 31. doi:10.1001/jamacardio.2017.5250. [Epub ahead of print] PubMed PMID: 29387880.

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 Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC August 20, 2014.

Hicks et al. 2018
Hicks KA, Mahaffey KW, Mehran R, Nissen SE, et alCardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021–34

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

Iwaz et al 2016
Iwaz JA, Le E, Aramin H, Romero D, Iqbal N, Kawahara M, et al. New targets in the drug treatment of heart failure. Drugs 2016;79:187-201.

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

Kosiborod et al 2017a
Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al, on behalf of the CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study. Circulation 2017 May 18. pii: CIRCULATIONAHA.117.029190. doi: 10.1161/CIRCULATIONAHA.117.029190. [Epub ahead of print]

Kosiborod et al 2017b
Kosiborod M, Gause-Nilsson I, J 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 2017;31(7):1215-21.

Kristensen et al 2015
Kristensen SL, Jhund PS, Køber L, McKelvie RS, Zile MR, Anand IS, et al. Relative importance of history of heart failure hospitalisation and N-terminal Pro–B-type natriuretic peptide level as predictors of outcomes in patients With heart failure and preserved ejection fraction. JACC Heart Fail 2015 Jun;3(6):478-86.

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.

Kristensen et al 2017
Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D1, Win S, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation. 201721;135(8):724-35.

Lam et al 2011
Lam CSP, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. European Journal of Heart Failure 2011; 13: 18–28.

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.

Neal et al 2017
Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al, for the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. 2017; 377: 644-657.

Oktay et al 2013
Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep 2013;10(4):401-10.

Okumura et al 2016
Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ; 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 Jun 7;133(23):2254-62. doi: 10.1161/CIRCULATIONAHA.115.020729. Epub 2016 Apr 20. PubMed PMID: 27143684.Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep 2013;10(4):401-10.

Ott et al 2017
Ott C, Jumar A, Striepe K, Friedrich S, Karg MV, Bramlage P, et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. Cardiovasc Diabetol 2017;16:26.

Pfeffer et al 2015
Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation. 2015;131:34-42.

Rådholm et al 2018
Rådholm K, Figtree, Perkovic V, Solomon SD, Mahaffey KW, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation. 2018;137 https://doi.org/10.1161/CIRCULATIONAHA.118.034222

Shigiyama et al 2017
Shigiyama F, Kumashiro N, Miyagi M, Ikehara K, Kanda E, Uchino H, et al. Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. Cardiovasc Diabetol 2017;16:84. DOI 10.1186/s12933-017-0564-0.

Skali et al 2014
Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R, Kukin M, Lichstein E, McNitt S, Moss AJ, Pfeffer MA, Solomon SD. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. Eur J Heart Fail. 2014 May;16(5):560-5. doi: 10.1002/ejhf.71. Epub 2014 Feb 27. PubMed PMID: 24578164.

Solomon et al 2005
Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA; Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005 Dec 13;112(24):3738-44

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

Thygesen et al 2012
Thygesen Kristian, Alpert Joseph S., Jaffe Allan S., Simoons Maarten L, Chaitman ,White Harvey D. Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal

Definition of Myocardial Infarction. Third Universal Definition of Myocardial Infarction. Global Heart Vol: 7 (4), 2012 Page: 275-295

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

Zannad et al 2014
Zannad F Garcia AA, Anker SD Armstrong PW Calvo G et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. Eur J Heart Failure 2013;15:1082–94.

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.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

A subject who is rescreened is not required to sign another ICF.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

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 committee and 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 regards 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 nonvoting members of the Sponsor, and will operate under an Executive Committee charter.

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.

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.

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.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event 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-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the subject 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 subject'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).

B 4 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 subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

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 subject or may require medical treatment 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 (e.g. neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 Appendix B 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 Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When assessing 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 subject 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.

B 8 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 investigational product that either causes harm to the participant or has the potential to cause harm to the participant.

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 participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant 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 participant
- 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 participant received the medication (excluding IxRS errors)
- Wrong drug administered to participant (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
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant 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.

Appendix C Cardiovascular related events

C 1 Myocardial Infractions (MI)

MIs are not endpoints in this study but unstable angina and myocardial infarction should be recorded as SAEs if serious criteria are met and additional information be collected in specific eCRF. The diagnoses of unstable angina and MI should adhere to the standardised definitions for endpoints (Hicks et al 2018) described in Appendix C 2

C 2 Diagnosis of MI and Unstable Angina

Myocardial infarction (MI)

The diagnosis of an MI should be made according to standard clinical practice but is expected to align with the criteria from Third Universal Definition of MI, i.e. detection of a rise and/or fall of cardiac biomarkers such as troponin and at least one of the following: typical clinical symptoms, ischaemic ECG findings, imaging evidence of myocardial injury, or detection of an intracoronary thrombus by angiography or autopsy (Thygesen et al 2012).

The diagnosis should be made by, or in consultation with, a cardiologist. The findings supporting the diagnosis should be documented in the description of the SAE in the eCRF.

Unstable Angina (UA)

Unstable Angina (UA) is not an endpoint in this study but should be recorded as SAEs (and DAEs when appropriate). The diagnosis of an UA should be made according to standard clinical practice but is expected to align with the following definition:

The diagnosis of unstable angina will require ischemic chest pain (or equivalent) at rest ≥10 minutes in duration considered to be myocardial ischemia upon final diagnosis and prompting hospitalisation within 24 hours of the most recent symptoms, and without elevation in cardiac biomarkers of necrosis, and the presence of objective evidence of ischemia as defined by at least 1 of the following criteria:

1. New or worsening ST or T wave changes in ≥2 anatomically contiguous leads on a resting ECG (in the absence of LVH and LBBB):

a) transient (<20 minutes) ST elevation at the J point ≥ 0.2 mV in men (> 0.25 mV in men < 40 years old) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads, or

b) horizontal or down-sloping ST depression ≥ 0.10 mV, or

c) T-wave inversion ≥ 0.2 mV

2. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs.

3. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

C 3 Stroke

Stroke is not an endpoint in this study but should be recorded as SAEs if serious criteria are met, with additional information e.g. classification of stroke type (ischaemic, haemorrhagic, or undetermined) collected in a specific eCRF.

The diagnosis of stroke should be made according to standard clinical practice and align with the definition for stroke in the standardized definitions for endpoints (Hicks et al. 2018 Hicks KA, Mahaffey KW, Mehran R, Nissen SE, et alCardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021–34) described in Appendix C 4 and be differentiated vs Transient Ischaemic Attack (TIA).

C 4 Definition of Stroke and Transient Ischemic Attack

The distinction between an Ischemic Stroke and a Transient Ischemic Attack is the presence of infarction. Persistence of symptoms ≥24 hours or until death[3] is an acceptable indicator of acute infarction in the absence of imaging evidence of infarction.

Transient Ischemic Attack
Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction.

Stroke
Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
Haemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with haemorrhagic transformation and not a haemorrhagic stroke.

B. Haemorrhagic Stroke

Haemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by non-traumatic intraparenchymal, intraventricular, or subarachnoid haemorrhage. NOTE: Subdural hematomas are intracranial haemorrhagic events and not strokes.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction but with insufficient information to allow categorization as either ischemic or haemorrhagic.

References:

Hicks KA et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021–34 https://doi.org/10.1016/j.jacc.2017.12.048

Draft Definitions for CDISC August 20, 2014

Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MSV, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee J-M, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064-2089.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the subject´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on heart failure with preserved ejection fraction continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject decline to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and** Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:
Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section **Error! Reference source not found.** of the main Clinical Study Protocol.

Collection of samples for genetic research
The blood sample for genetic research will be obtained from the subjects at Visit 2. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples
The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely withdrawal from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal

statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Handling of Human Biological Samples

E 1 Chain of custody of biological samples

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

The Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

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 will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

E 2 Withdrawal of Informed Consent for donated biological samples

If a subject 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 the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

E 3 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 (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations 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 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 (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- **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 G Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law (not applicable)

Appendix H Medical device incidents: definition and procedures for recording, evaluating, follow-up, and reporting (not applicable)

Appendix I Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
BP	Blood Pressure
CEA	Clinical Event Adjudication
COPD	Chronic Obstructive Pulmonary Disease
CSA	Clinical study Agreement
CV	Cardiovascular
DAE	Adverse Event leading to discontinuation of investigational product
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDC	Electronic Data Capture
EHRs	Electronic Health Records
FAS	Full Analysis Set
GCP	Good Clinical Practice
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HR	Hazard Ratio
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.
IxRS	Interactive Voice/Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAE	Left Atrial Enlargement
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
NYHA	New York Heart Association

Abbreviation or special term	Explanation
PACD	Primary Analysis Censoring Date
PTDV	Premature Treatment Discontinuation Visit
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCV	Study Closure Visit
SoA	Schedule of Activities
T2D	Type 2 Diabetes Mellitus

Appendix J New York Heart Association (NYHA) Functional Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (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 K The KC Cardiomyopathy Questionnaire

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 stopping	❑	❑	❑	❑	❑	❑
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 past 2 weeks, 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 past 2 weeks, 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 per 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 your 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 weeks.

Please 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 relationships with loved ones	❑	❑	❑	❑	❑	❑

 Original US English

Appendix L EQ-5D-5L Questionnaire

Health Questionnaire

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

MOBILITY

I have no problems walking ❑

I have slight problems walking ❑

I have moderate problems walking ❑

I have severe problems walking ❑

I am unable to walk ❑

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 ❑

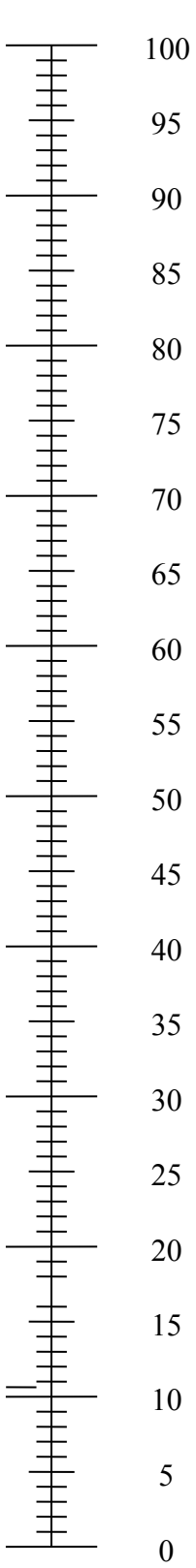
I am moderately anxious or depressed ❑

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 best health you can imagine.
  0 means the worst 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 = ☐



Appendix M Patient Global Impression of Severity for Heart Failure Symptoms

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

Clinical Study Protocol

Drug Substance	Dapagliflozin
Study Code	D169CC00001
Version	4.0
Date	12th November 2020

An International, Double-blind, Randomised, Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

DELIVER - Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

Eudra CT number: 2018-000802-46

VERSION HISTORY

Version 1.0, 24th April 2018				
Initial creation				
Version 2.0, 09th May 2018				
	Section changed	**Previous Version**	**Current Version**	**Reason for change**
1.	Title page	**Regulatory Agency Identifying Number(s):**	**Regulatory Agency Identifying Number(s):** **Eudra CT number:** 2018-000802-46	Missing information added
2.	Appendix A – Section A3	A subject who is rescreened is **not** required to sign another ICF.	A subject who is rescreened is required to sign another ICF.	Correction of typo error
3.	Appendix D – Section D2 Correction of cross referencing error	**Withdrawal of consent for genetic research:** Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.	**Withdrawal of consent for genetic research:** Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.	Cross-reference link was updated
4.	Mislabelling of Appendices	Mislabelling of Appendices A, B, C, D, E, G, H, I, J, K, L, M	Correction of mislabelling of Appendices A, B, C, D, E, **F**, G, H, I, J, K, L	Typo error

Version 3.0, 16th December 2019		
	Section changed	**Summary of change**
1.	1.2 Synopsis	CSP synopsis was modified to adjust the study sample size from original 4700 to approximately 6100, based on ongoing blinded monitoring of events accrual. Accordingly, the anticipated recruitment period was increased from 18 months to 22 months.
2.	4.1 Overall design	Overall design was modified to adjust the sample size increase as below: "It is estimated that approximately 11000 patients at approximately 400-500 sites in 20-25 countries will be enrolled to reach approximately 6100 randomised patients."
3	4.2 Scientific rationale for study design	The subacute subgroup definition was modified, such that the recent discharge date from hospitalisation for heart failure was extended from 21 days to 30 days, to be more aligned with clinical practice, i.e.: "…to address a specific need in a period with high risk for events, a proportion of patients will be enrolled and randomised during hospitalisation for heart failure or within 30 days of discharge from hospitalisation for heart failure (subacute subgroup)."
4.	6.3.1.2 Capping	The definition of subacute subgroup (one of the potential capping factors) was modified the same as above.
5.	9.2 Sample size determination	Statistical section 9.2 was updated to reflect the sample size increase in detail. Specifically: "Based on the ongoing blinded monitoring of event accrual (including the percentage of patients from the sub-acute category), the sample size is increased from original 4700 to approximately 6100 randomised patients to provide the required number of 844 patients with a primary event. Accordingly, the recruitment period is anticipated to increase from the original 18 months to 22 months. The study is event driven and the number of patients or duration may further change."

Version 4.0, 12th November 2020

	Section changed	Summary of change
1.	1.1: Schedule of Activities (SoA)	Concomitant Medication check was added to Visit 1 (Enrolment) to clarify screening eligibility checks. Clarification to BP, pulse, weight and creatinine assessments at Visit 6 and 7 - onwards added: "Assessments to be repeated every 12 months (Visit 6, Visit 9, Visit 12)". Recording of COVID-19 testing results from Visit 2 onwards added to Safety Events.
2.	1.2 Synopsis	Primary objective and first secondary objective were updated to include analysis of both the full study population and the subpopulation with LVEF <60%. Urgent HF visits were added in addition to hospitalizations for HF as recurrent HF events to be evaluated for the first secondary objective. "To determine whether dapagliflozin is superior to placebo in reducing CV death" added to secondary objectives. "To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA class" moved from secondary to exploratory objectives. "To compare the effect of dapagliflozin versus placebo on health status assessed by Patient global impression of severity (PGIS) questionnaires" removed. Table 2 corrected accordingly. Exploratory objective "To compare the effect of dapagliflozin versus placebo on EuroQol five-dimensional five-level questionnaire (EQ- 5D-5L)" was updated to: "To describe health status assessed by EuroQol five-dimensional five-level questionnaire (EQ- 5D-5L)". Estimated date of last patient completed changed to: Q4 2021. Study duration was prolonged to 39 months. Number of primary endpoint events changed from 844 to 1117. Recruitment period prolonged up to 29 months. Statistical methods section updated to reflect the changes to the primary objective, multiple testing procedure and the increased event target.
3.	2.1 Study Rationale	Section updated to reflect current amendment changes about the two hypotheses, that dapagliflozin is superior to placebo in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function (LVEF >40%), with or without T2D, in (1) the full population and in (2) an LVEF <60% subpopulation.
4.	4.1 Overall Design	Number of primary endpoints updated to 1117. Anticipated total study duration time updated to 39 months. It was added that Study Closure Visit (SCV) which should be hold within 6 weeks of the PACD, can be extended if decided by Global Study Team.
5.	4.2 Scientific rationale for study design	New paragraph added to justify the added testing of the treatment effect in patients with LVEF <60.

6.	8. Study Assessments and Procedures	It was clarified that during Visit 1, the investigator assesses patient's eligibility criteria and reviews concomitant medications, and relevant medications will be recorded. COVID-19 testing was added to Safety events assessment during Visits: 3,4,5,6,7 and onwards, as well as Premature Treatment Discontinuation Visit and Study Closure Visit. It was clarified that starting from Visit 6, vital signs (BP, pulse), and weight assessment as well as blood samples collection for creatinine (for calculation of eGFR) will be repeated every 12 months - on Visit 6, Visit 9 and Visit 12.
7.	8.3 Efficacy Assessments	An alternative phone collection mode solution was implemented for the administration of electronic PROs in settings that are affected by COVID-19 pandemic.
8.	8.4 Safety Assessments	COVID-19 testing results recording was added into Other safety assessments.
9.	8.5 Collection of adverse events	The process of Adjudication of potential DKA events by an independent DKA Committee was implemented (section 8.5.1.2.2.) Requirements for capturing of Major hypoglycaemic events were added as section 8.5.1.4.
10.	9.2 Sample size determination	Section updated to reflect the dual primary hypothesis, changed multiple testing procedure and increased event target.
11.	9.3 Populations for analysis	A subset of the full analysis set consisting of patients with baseline LVEF of <60% (or LVEF <60% subpopulation) will be analysed separately as part of the confirmatory statistical testing procedure added to full analysis set.
12.	9.4 Statistical Analyses	Analysis of the primary variable updated with dual primary analysis. Analysis of the secondary variables updated with regard to analysis of recurrent HF events and CV death for the LVEF < 60 subpopulation, and addition of time to CV death as a secondary endpoint. Methods for multiplicity control updated according to the dual primary hypotheses and updated testing procedure.
13.	9.5 Interim Analyses	Clarification added that the interim analysis testing will be done in the full study population. Futility analysis was removed.

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Study of Assessments

Visit	**1 Enrolment**	**2 Randomisation**	**3**	**4**	**5**	**6**	**7 – onwards**	**Premature Treatment Discontinuation Visit**	**Study Closure Visit**	**For details see Section:**
Day/Month	**Day -21 to Day -1**	**Day 1**	**Day 30 (±7)**	**Day 120 (±7)**	**Day 240 (±7)**	**Day 360 (±7)**	**Day 480 - onwards (every 120 days ±14 days)**		**≤ 6 weeks after PACD**	
Informed consent	X[6]									5.1, A 3
Inclusion/exclusion criteria	X	X								5.1, 5.2
Demographics	X									5.1
Medical history	X	X								5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	6.5
Cardiac and HF related procedures			X	X	X	X	X	X	X	8.5.1.3
Physical exam	X	X							X	8.4.1
Systolic and diastolic BP	X	X	X			X[3]	X[3]	X	X	5.2, 8.4.2
Pulse	X	X	X			X[3]	X[3]	X	X	5.2, 8.4.2
Weight	X					X[3]	X[3]	X	X	8.4.6.1
Height	X									8.4.6.1
NYHA classification	X	X	X	X	X			X	X	5.1, Appendix I
12-lead ECG	X									8.4.3

Visit	**1 Enrolment**	**2 Randomisation**	**3**	**4**	**5**	**6**	**7 – onwards**	**Premature Treatment Discontinuation Visit**	**Study Closure Visit**	**For details see Section:**
Day/Month	**Day -21 to Day -1**	**Day 1**	**Day 30 (±7)**	**Day 120 (±7)**	**Day 240 (±7)**	**Day 360 (±7)**	**Day 480 - onwards (every 120 days ±14 days)**		**≤ 6 weeks after PACD**	
C-lab NT-proBNP	X									5.1
C-lab eGFR (creatinine)	X		X	X		X[3]	X[3]			5.2, 8.4.4
C-lab HbA1c	X									6.3.1.1
Sample for genetic research, if applicable[5]		X								Appendix D
KCCQ		X[4]	X[4]	X[4]	X[4]			X[4]	X[4]	8.3.3.1
PGIS		X[4]	X[4]	X[4]	X[4]			X[4]	X[4]	8.3.3.2
EQ-5D-5L		X[4]			X[4]			X[4]	X[4]	8.3.3.3
Local pregnancy test (female patients with childbearing potential only)		X								5.1
Randomisation		X								8.2.1
Dispense investigational product (IP)		X		X	X	X	X			6
Collect unused IP; check IP compliance				X	X	X	X	X	X	6

Visit	**1 Enrolment**	**2 Randomisation**	**3**	**4**	**5**	**6**	**7 – onwards**	**Premature Treatment Discontinuation Visit**	**Study Closure Visit**	**For details see Section:**
Day/Month	**Day -21 to Day -1**	**Day 1**	**Day 30 (±7)**	**Day 120 (±7)**	**Day 240 (±7)**	**Day 360 (±7)**	**Day 480 - onwards (every 120 days ±14 days)**		**≤ 6 weeks after PACD**	
Efficacy events (death and worsening heart failure) [1]		X[1]	X	X	X	X	X	X	X	8.3
Safety events[2,7]	X	X	X	X	X	X	X	X	X	8.4

AEs Adverse events; DAEs Adverse events leading to discontinuation of investigational product; PACD Primary Analysis Censoring Date; SAEs Serious adverse events; C-lab Central laboratory

[1] Efficacy events are considered as endpoints from time of randomisation and throughout the study. Prior to randomisation, these events are considered as SAEs.

[2] SAEs will be recorded from the time of informed consent. DAEs and Amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs will be recorded from Visit 2 onwards.

[3] Assessments to be repeated every 12 months (Visit 6, Visit 9, Visit 12).

[4]Will be administered using a site-based electronic device. It is preferred that PRO questionnaires are completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions

[5]Blood sample for future genetic research is optional. The genetic sampling is subject to separate consent by the patient.

[6]The Patient signs the ICF. Patients who agree to the optional sampling of blood for genetic research will provide their consent.

[7]Including recording of COVID-19 testing results from Visit 2 onwards.

1.2 Synopsis

International coordinating Investigator

Scott D. Solomon, MD

[redacted]
Harvard Medical School
[redacted]
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115
US

Protocol Title:

An International, Double-blind, Randomised Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF).

Rationale:

The prevalence of chronic heart failure (HF) continues to increase globally, and the annual global economic burden (several hundred billion dollars in 2012) will increase as the population ages. Approximately half of all heart failure patients have heart failure with preserved ejection fraction (HFpEF) representing a particularly significant unmet need given that no approved pharmacotherapy exists specifically for this condition. Patients with HFpEF generally receive diuretic treatment for symptom relief, and should receive guideline recommended therapies for concomitant diseases such as hypertension. Recent data from cardiovascular (CV) outcome trials of SGLT2 inhibitors (empagliflozin and canagliflozin) and real world studies (including patients treated with dapagliflozin) indicate that treatment with SGLT2 inhibitors can reduce the risk of CV death and hospitalisation due to HF in patients with Type 2 Diabetes (T2D) overall and in patients with T2D and concomitant HF. Limitations associated with the randomised clinical trials as well as the observational studies are that only patients with T2D were studied, and that the proportion of patients with HFrEF and HFpEF, respectively, is unknown. This study will test the hypothesis that dapagliflozin will reduce the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function (LVEF >40%), with or without T2D.

Table 2 Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function in • full study population • subpopulation with LVEF <60%	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF 3. Urgent HF visit (e.g., emergency department or outpatients visit)
Secondary objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in reducing the total number of HF events (hospitalisation for HF or urgent HF visit) and CV death in • full study population • subpopulation with LVEF <60%	Total number of HF events (first and recurrent) and CV death
To determine whether dapagliflozin is superior to placebo in improving Patient Reported Outcomes measured by KCCQ	Change from baseline in the total symptom score (TSS) of the KCCQ at 8 months
To determine whether dapagliflozin is superior to placebo in reducing CV death	Time to the occurrence of CV death
To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality	Time to the occurrence of death from any cause
Safety objective:	
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF	Serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs), amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs
Exploratory Objective:	
To determine whether dapagliflozin is superior to placebo in reducing all-cause hospitalisation	Time to the first occurrence of hospitalisation from any cause

To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA class	Proportion of patients with worsened NYHA class from baseline to 8 months
To describe health status assessed by EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment	Results will be reported separately in a health economic report
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 have an effect on eGFR.	Change in eGFR from baseline
To explore whether dapagliflozin compared to placebo improves KCCQ summary scores, subscores of TSS (Symptom frequency and symptom burden) and domains	Change in Clinical summary score, TSS subscores, Overall summary score, QoL score
To collect and store blood samples for future exploratory genetic research	Not applicable. Results will be reported separately

BP Blood pressure; CV Cardiovascular; EQ-5D-5L EuroQol five-dimensional five-level questionnaire
HF Heart failure; HFrEF Heart failure with reduced ejection fraction; KCCQ Kansas City Cardiomyopathy Questionnaire NYHA New York Heart Association

Overall design:

This is an international, multicentre, parallel-group, event-driven, randomised, double- blind study in patients with HFpEF, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background regional standard of care therapy, including treatments to control co- morbidities, in reducing the composite of CV death and heart failure events (hospitalisations for HF or urgent HF visits). Adult patients aged ≥40 years with HFpEF (LVEF >40% and evidence of structural heart disease) and New York Heart Association (NYHA) class II-IV who are eligible according to the inclusion/exclusion criteria will be randomised in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo. Both out-patients and in-patients hospitalised for heart failure and off intravenous heart failure-therapy for 24 hours can be randomised. It is estimated that approximately 11000 patients at approximately 400-500 sites in 20-25 countries will need to be enrolled to reach approximately 6100 randomised patients.

Study Period:

Estimated date of first patient enrolled: Q3 2018

Estimated date of last patient completed: Q4 2021

Number of randomised Subjects: approximately 6100 patients

Treatments and treatment duration:

Patients will be randomised in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo once daily. The original anticipated average treatment duration was 24 months (range 15 to 33 months). With updated sample size and increased target number of events, the maximum treatment duration is expected to be approximately 39 months.

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will review accumulating trial data by treatment group in order to monitor patient safety and efficacy, ensure the validity and integrity of the trial, and make benefit-risk assessment.

Statistical methods

This study is event-driven with a target of 1117 patients with a primary endpoint event. The primary objective of the study is to determine the superiority of dapagliflozin versus placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit). Two hypotheses will be tested simultaneously (i.e, dual primary analyses) for this primary objective: (1) in the full population and in (2) an LVEF <60% subpopulation, with alpha allocated to each test. The final alpha split will be defined in the SAP prior to the interim analysis. It is anticipated that at least 70% of the events (i.e. approximately 780 events) will be available for the LVEF <60% subpopulation. To illustrate, assuming a true hazard ratio (HR) of 0.80 between dapagliflozin and placebo, a two-sided alpha of 1.5% would yield a power of 90% for the full population and a two-sided alpha of 2.4% would yield a power of 80% for the LVEF <60% subpopulation.

Based on above assumption and ongoing blinded monitoring of events accrual, approximately 6100 patients are estimated to provide the required number of primary events in the full population during an anticipated recruitment period up to 29 months and followed until the pre-specified number of primary events has occurred. Randomisation will be stratified by presence or absence of Type 2 Diabetes (T2D).

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, including events occurring on or prior to the primary analysis censoring date (PACD), 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. The p-value, hazard ratio and 95% confidence interval will be reported.

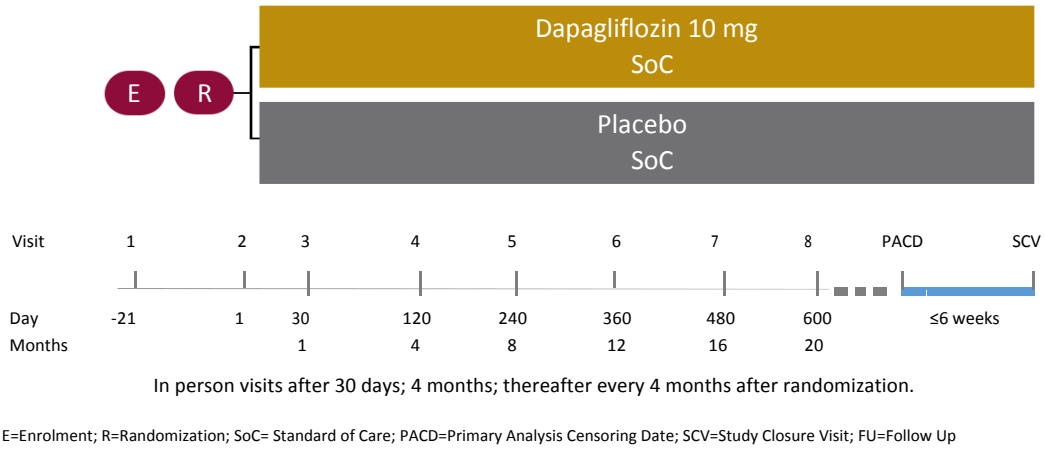
Interim analysis is planned to be performed including approximately 67% of target number of adjudicated primary endpoints.

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.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



E=Enrolment; R=Randomization; SoC= Standard of Care; PACD=Primary Analysis Censoring Date; SCV=Study Closure Visit; FU=Follow Up

2. INTRODUCTION

2.1 Study rationale

The prevalence of chronic HF continues to increase globally. An estimated 38 million people are affected worldwide (Braunwald 2015), with over 1 million hospitalisations annually in both 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); this will increase dramatically as the population ages.

Heart failure is a complex syndrome caused by structural and/or functional abnormalities. It is characterised by dyspnoea, fatigue, and pulmonary congestion and/or peripheral oedema due to fluid retention. Patients with signs and symptoms of HF are categorised, based on measurement of left-ventricular ejection fraction (LVEF), as having HF with reduced LVEF (HFrEF) or HF with preserved LVEF (HFpEF).

Approximately half of all heart failure patients have HFpEF (Oktay et al 2013). Risk of death for HFpEF patients is high, with annualised mortality rate up to 15% in community settings (Lam et al 2011). In controlled clinical trials, patients with HFpEF tend to be older and have a higher prevalence of hypertension as compared to patients with HFrEF, although major clinical outcomes are similarly dominated by CV death and HF hospitalisation, the yearly event rates appear to be lower than in HFrEF (Solomon et al 2005). However, patients with HFpEF have a particularly significant unmet medical need given that outcome studies hitherto performed have not resulted in any approved pharmacotherapy specifically for this condition. Conversely, outcome studies have provided evidence for treatments for HFrEF that hence can improve symptoms and haemodynamics as well as reduce hospitalisations for heart failure and mortality. These treatments include diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin II receptor blocker neprilysin inhibitors, mineralocorticoid receptor antagonists, and beta-blockers (Iwaz et al 2016).

Recent data from cardiovascular (CV) outcome trials of SGLT2 inhibitors (empagliflozin and canagliflozin) indicate that treatment with SGLT2 inhibitors can reduce the risk of CV death and hospitalisation due to HF in patients with T2D overall, and in patients with T2D and concomitant HF (Zinman et al 2015; Fitchett et al 2016; Neal et al 2017; Rådholm et al 2018).

Results from real-world observational studies are broadly consistent with the randomised clinical trials in supporting the benefits of SGLT2 inhibitors in reducing risk of HF hospitalisation and CV death. The CVD-REAL study, consisting of more than 300000 patients with T2D, both with and without established CV disease, across 6 countries found that patients treated with SGLT2 inhibitors compared to patients treated with other glucose lowering drugs was associated with a relative risk reduction in hospitalisation due to HF (39%), all-cause death (51%), and the composite of hospitalisation due to HF or CV death (46%) (Kosiborod et al 2017a).

Limitations associated with the randomised clinical trials as well as the observational studies are that only patients with T2D were studied, and that the proportion of patients with HFrEF and HFpEF, respectively, is unknown.

This study will simultaneously test the two hypotheses that dapagliflozin is superior to placebo in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function (LVEF >40%), with or without T2D, in (1) the full population and in (2) an LVEF <60% subpopulation.

2.2 Background

Dapagliflozin is a potent, highly selective and orally active inhibitor of human renal SGLT2. A detailed description of the chemistry, pharmacology, efficacy, and safety of dapagliflozin is provided in the Investigator's Brochure. Supporting the hypothesis that dapagliflozin may reduce CV Death and HF events in HF patients, irrespective of diabetes status, are observations from the overall dapagliflozin clinical development programme. Dapagliflozin lowers HbA1c with a low risk of inducing hypoglycaemia. In addition, dapagliflozin treatment has also been shown to reduce weight and systolic blood pressure, and to have favourable effect on increased blood uric acid, albuminuria, and arterial elasticity, conditions which are associated with increased CV and renal risk (Shigiyama et al 2017). Dapagliflozin is believed be nephroprotective through non-glycaemic mechanisms (Wanner et al 2016).

The identified blood pressure lowering effects, may reduce the primary outcome in a study population with high prevalence of hypertension, similarly, the observed effects on body weight, may be beneficial to the large part of the study population with obesity. The findings from EMPA-REG, with a similar SGLT2 inhibitor compound, suggests that kidney function is preserved, or improved in this diabetic study population. Furthermore, HFpEF patients are characterized by fluid retention and a change in cardiac metabolism favouring glucose as substrate, both of which has been hypothesised to be positively impacted by SGLT2 inhibitor treatment. Moreover, arterial stiffness, and abnormal ventriculo-arterial coupling, are common in patients with HFpEF, and may be modified by SGLT2 inhibitor treatments.

The clinical studies in healthy subjects at high multiple doses also show that, due to the mechanism of action, dapagliflozin does not induce hypoglycemia in nondiabetic subjects; however, pharmacodynamic effects on glucose, sodium, and urinary volume are observed. Therefore, the changes in these diabetes-independent mechanisms and intrarenal physiology are expected to be similar regardless of underlying disease.

This study is an international, multicentre, parallel-group, event-driven, randomised, double-blind, placebo-controlled study in HFpEF patients, evaluating the effect of dapagliflozin 10 mg, given once daily in addition to background regional standard of care therapy, including treatments to control co-morbidities, in reducing the composite of CV death and heart failure events (hospitalisations for HF or urgent HF visits).

2.3 Benefit/risk assessment

Dapagliflozin has global marketing approval in approximately 90 countries with the most recent estimate of cumulative post-marketing experience totalling over 1.6 million patient-years. Detailed information about the known and expected benefits and risks and reasonably expected adverse events of dapagliflozin appears in the Investigator's Brochure. The following is a summary of benefit-risk considerations relevant to the HFpEF target population.

2.3.1 Potential risks to patients

Dapagliflozin reduces blood volume and blood pressure from its diuretic effect, which could be a concern in patients with HFpEF, but also be important mechanisms of a potential treatment effect. However, in the dapagliflozin type 2 diabetes mellitus (T2D) program, the rate of events related to volume depletion and impaired renal function have been similar between dapagliflozin and placebo. Loop-diuretics are widely used in the target patient population and are also allowed in this study. A pooled analysis of patients with T2D and HF in the dapagliflozin development program, showed no increase of volume depletion events but increase in renal events, mainly creatinine increases, in patients treated with dapagliflozin (n=171) compared with placebo treated patients (n=149). About half of the patients were on loop diuretics (Kosiborod et al 2017b).

An increase in amputations, mostly affecting toes, was observed in a clinical trial (Neal et al 2017) with another SGLT2 inhibitor. There is no indication from the clinical development program that dapagliflozin is associated with an increased risk of amputation (see Section 8.5.1.1 for the detection and capture of amputation events).

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.

There have been post-marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with T2D taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected interruption of dapagliflozin treatment should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., T1D, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in patients in these circumstances. Dapagliflozin is currently not indicated for the treatment of patients with T1D; these patients are excluded from this study.

2.3.1.1 Protection against risks

This study has been designed with appropriate measures in place to monitor and minimise any potential risks to participating patients. Data regarding amputations and adverse events potentially placing the patient at risk for a lower limb amputation will be collected (see Section 8.5.1.1). 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 (see Section 9.5.1).

2.3.2 Potential benefits to patients

All patients in the study are expected to be optimally treated according to regional standard of care therapy, including treatments to control co-morbidities, and dapagliflozin or placebo will be administered on top of this treatment.

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.

2.3.3 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 eligible patients. Although hypothesis-generating data suggest beneficial effects of SGLT2 inhibitors in patients with T2D with heart failure, at the time of writing of this clinical study protocol, no available SGLT2 inhibitor has a treatment indication for patients with HFpEF. The proposed clinical study will test the hypothesis that dapagliflozin reduces the risk of CV death and HF events in patients with HFpEF, with or without T2D, in a rigorous fashion. The results could potentially offer substantial benefit to patients with HFpEF, a patient population with a large medical need for effective treatments.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function in • full study population • subpopulation with LVEF <60%	Time to the first occurrence of any of the components of this composite: 4. CV death 5. Hospitalisation for HF 6. Urgent HF visit (e.g., emergency department or outpatients visit)
Secondary objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in reducing the total number of HF events (hospitalisation for HF or urgent HF visit) and CV death in • full study population • subpopulation with LVEF <60%	Total number of HF events (first and recurrent) and CV death
To determine whether dapagliflozin is superior to placebo in improving Patient Reported Outcomes measured by KCCQ	Change from baseline in the total symptom score (TSS) of the KCCQ at 8 months
To determine whether dapagliflozin is superior to placebo in reducing CV death	Time to the occurrence of CV death
To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality	Time to the occurrence of death from any cause
Safety objective:	
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF	Serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs), amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs
Exploratory Objective:	
To determine whether dapagliflozin is superior to placebo in reducing all-cause hospitalisation	Time to the first occurrence of hospitalisation from any cause

To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA class	Proportion of patients with worsened NYHA class from baseline to 8 months
To describe health status assessed by EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment	Results will be reported separately in a health economic report
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 have an effect on eGFR.	Change in eGFR from baseline
To explore whether dapagliflozin compared to placebo improves KCCQ summary scores, subscores of TSS (Symptom frequency and symptom burden) and domains	Change in Clinical summary score, TSS subscores, Overall summary score, QoL score
To collect and store blood samples for future exploratory genetic research	Not applicable. Results will be reported separately

BP Blood pressure; CV Cardiovascular; EQ-5D-5L EuroQol five-dimensional five-level questionnaire
HF Heart failure; HFrEF Heart failure with reduced ejection fraction; KCCQ Kansas City Cardiomyopathy Questionnaire NYHA New York Heart Association

4. STUDY DESIGN

4.1 Overall design

This is an international, multicentre, parallel-group, event-driven, randomised, double-blind, placebo-controlled study in HFpEF patients, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background regional standard of care therapy, including treatments to control co-morbidities, in reducing the composite of CV death or heart failure events.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

Adult patients with HFpEF (defined for the purposes of this study as LVEF >40% and evidence of structural heart disease) aged ≥40 years and with NYHA class II- IV who meet the inclusion criteria, and none of the exclusion criteria, will be randomised in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo. Randomised treatment should be started as soon as possible and within 24 hours after randomisation. It is estimated that approximately 11000 patients at approximately 400-500 sites in 20-25 countries will be enrolled to reach approximately 6100 randomised patients (see Section 9.2).

Study closure procedures will be initiated when the predetermined number of primary endpoints are predicted to have occurred (n=1117), i.e. the Primary Analysis Censoring Date (PACD). Patients should be scheduled for a Study Closure Visit (SCV) within 6 weeks of the PACD, which can be extended if decided by Global Study Team. The anticipated total study duration is approximately 39 months dependent on randomisation rate and event rate. The study duration, and the number of patients, may be changed if the randomisation rate or the event rate is different than anticipated. The study may be terminated early if a clear harmful effect of the study treatment is detected during the DMC review, or due to DMC recommendations following pre-specified interim analyses (see Section 9.5).

Data on baseline characteristics, endpoints and AEs will be collected through a validated electronic data capture (EDC) system with electronic case report forms (eCRFs).

4.2 Scientific rationale for study design

This is a randomised, multi-centre, double-blind, parallel-group study. Randomisation and double-blinding will minimise potential bias. The target population includes adult (aged ≥ 40 years) male and female patients with HFpEF, which is defined in this study as individuals with an established diagnosis of heart failure and a LVEF >40% and structural heart disease who meet natriuretic peptide thresholds. The requirement of demonstrated structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement[1]) and elevated natriuretic peptides aims to support the diagnosis of heart failure, since other common co-morbidities may cause overlapping symptoms. Most randomised patients will be out-patients. However, to address a specific need in a period with high risk for events, a proportion of patients will be enrolled and randomised during hospitalisation for heart failure or within 30 days of discharge from hospitalisation for heart failure (subacute subgroup).

The study population will include patients both with and without T2D, as the beneficial haemodynamic effects of dapagliflozin appear to be independent of the glycaemic effect, and can therefore be expected in both groups. Enrolment in the study may be capped based on the proportion of patients with/without T2D, in certain LVEF categories, in each NYHA class, with/without atrial fibrillation, randomised during or early after HF hospitalisation (subacute subgroup), and geographic region.

The control group will receive placebo; there are no approved pharmacological treatments for HFpEF that could be utilised as a comparator. All patients will be treated according to local guidelines on standard of care treatment for patients with HFpEF, focusing on treatment of HF symptoms (e.g. diuretics) and comorbidities (including treatment for high blood pressure, ischaemic heart disease, atrial fibrillation).

The study population will include patients with eGFR ≥ 25 ml/min/1.73m^2. Patients with reduced renal function have a clinical picture with increased intra-glomerular pressure, hypertension, proteinuria and fluid/sodium overload and SGLT2 inhibition can improve all these abnormalities through metabolic-independent mechanisms. Thus, patients with heart failure and reduced renal function could be expected to benefit from treatment with dapagliflozin.

The primary efficacy endpoints of the study are adjudicated CV death and HF events (hospitalisation for HF or urgent HF visit). The rationale for selecting CV death over all-cause death is the expectation that HF treatment will decrease CV death and not all potential causes of death (Zannad et al 2014). Heart failure events include both HF hospitalisations and unplanned HF visits requiring urgent treatment independently of whether the exacerbation of HF results in hospitalisation (according to CDISC definitions; Hicks et al 2014; Hicks et al 2018). These are the same endpoint definitions currently employed in the Sponsor's HFrEF outcome study (Dapa-HF; Study D1699C00001).

[1] Left Atrial Enlargement defined by at least 1 of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm^2 or LA volume ≥55 mL or LA volume index ≥29 mL/m

[2] Left Ventricular Hypertrophy defined by septal thickness or posterior wall thickness ≥1.1 cm

The rationale for including outpatient 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. As stated in EMA Guidance 2016, '…patient are often managed for episodes of transient decompensation or worsening HF in outpatient settings (eg, emergency departments, observation units, other outpatient settings). The capture of events of worsening HF without hospitalisation may be warranted as an additional endpoint.' Including only hospital admissions is likely to overlook a modest but significant proportion of episodes of worsening HF (Skali et al 2014, Okumura et al 2016, Greene et al 2018).

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 the treatment effects on 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 (Greene et al 2018, Spertus et al 2005).

There has been a gradual accumulation of data that HF patients with mildly abnormal (or "mid-range") ejection fraction (LVEF 40-50%), although traditionally classified as HFpEF, may potentially benefit from therapies that have been shown to improve outcomes in HFrEF (Nauta et al 2017). During the course of the DELIVER trial, the PARAGON-HF trial was completed, randomizing patients with HFpEF to sacubitril/valsartan or valsartan alone. While the study failed to meet its primary objective (Solomon et al 2019), there appeared to be a differential treatment effect by LVEF with benefit largely seen in patients with LVEF 45-60% (Solomon et al 2020). This new data suggests that HFpEF with a high-normal LVEF may constitute different clinical entities than heart failure with low-normal or mildly reduced LVEF (Lam et al 2020). To account for this emerging information in DELIVER, it was decided to formally investigate the treatment effect in both the subset of patients with LVEF<60% and in the full study population.

4.3 Justification for dose

The 10 mg dose of dapagliflozin has a well-characterised efficacy and safety profile in the T2D clinical development program and is the recommended dose in the majority of countries worldwide.

From a pharmacokinetic perspective, the currently approved dapagliflozin dose of 10 mg once daily is appropriate for use in patients with HFpEF. Slightly higher systemic exposure to dapagliflozin is expected in HFpEF patients when symptomatic, based on the dual renal and hepatic metabolism of dapagliflozin and the lower perfusion of these organs in this patient group. However, the increase in systemic exposure of 10 mg dapagliflozin is not anticipated to warrant dose adjustment in HF patients. Moreover, the anticipated slightly higher systemic exposure to dapagliflozin is likely to be beneficial in HF patients, by compensating for the reduced renal perfusion and consequently lower renal glucose and sodium filtered loads in these patients. Doses lower than 10 mg are therefore unlikely to provide as much benefit to patients with HF as the 10-mg dose. Lastly, no changes in dose of concomitant medications in the HFpEF population are

needed due to a lack of clinically meaningful drug-drug interactions for dapagliflozin with current medications used for treatment of patients with HFpEF, including standard of care medications used to control co-morbidities in this patient group.

In the dapagliflozin clinical program, there are no dose-related SAEs that preclude the use of 10 mg as a preferred dose. Additionally, in a post-hoc analysis of data from 320 patients with a documented history of HF and concomitant T2D in placebo-controlled clinical trials, dapagliflozin 10 mg was found to be well tolerated in this population (Kosiborod et al 2017b).

There are mechanistic reasons for choosing the 10-mg dose as well. One hypothesis of underlying pathophysiology in HFpEF is abnormal pressure coupling between the left ventricle and aorta, and drugs that reduce aortic stiffness may have beneficial effects in patients with HFpEF (Borlaug and Paulus 2011). Studies examining the highest approved dose for empagliflozin have reported improvements in aortic elasticity (Chilton et al 2015,Cherney et al 2014); similar studies are ongoing with dapagliflozin. In a completed placebo-controlled study, treatment with dapagliflozin 10 mg resulted in improvements in parameters associated with arterial remodelling in addition to lowering blood pressure in patients with T2D (Ott et al 2017). This prior work suggests that selecting the 10-mg dose of dapagliflozin is reasonable from a mechanistic perspective to demonstrate a clinical effect.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

The study may be terminated at individual study sites if the study procedures are not being performed according to GCP, or if no patients are recruited. Patients from terminated sites will have the opportunity to be transferred to another site to continue the study. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin, or due to recommendation by the DMC. Regardless of the reason for termination, all data required by the protocol at the time of discontinuation of follow-up will be collected. In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

In this protocol, 'enrolled' patients are defined as those who sign the informed consent form (ICF) and received E-Code. The ICF process is described in Appendix A 3. 'Randomised' patients are defined as those who undergo randomisation and receive a randomisation code.

Patients are eligible to be randomised in the study only if all of the following inclusion criteria and none of the exclusion criteria apply. Enrolled patients who for any reason are not randomised are considered screen failures (see Section 5.4).

5.1 Inclusion criteria

Subjects are eligible to be randomised in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Provision of signed informed consent prior to any study specific procedures.
2. Male or female patients age ≥40 years.
3. Documented diagnosis of symptomatic heart failure (NYHA class II-IV) at enrolment, and a medical history of typical symptoms/signs[2] of heart failure ≥6 weeks before enrolment with at least intermittent need for diuretic treatment.
4. Left Ventricular Ejection Fraction (LVEF) >40% and evidence of structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement[3]) documented by the most recent echocardiogram, and/or cardiac MR within the last 12 months prior to enrolment. For patients with prior acute cardiac events or procedures that may reduce LVEF, e.g. as defined in exclusion criterion 6, qualifying cardiac imaging assessment at least 12 weeks following the procedure/event is required.
5. NT-pro BNP ≥300 pg/ml at Visit 1 for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at Visit 1, NT-pro BNP must be ≥600 pg/mL.
6. Patients may be ambulatory, or hospitalized; patients must be off intravenous heart failure therapy (including diuretics) for at least 12 hours prior to enrolment and 24 hours prior to randomisation.

[2] Typical symptoms associated with heart failure: breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, ankle swelling;
Signs associated with Heart Failure:
More specific: elevated jugular venous pressure, hepatojugular reflex, third heart sound (gallop rhythm), laterally displaced apical impulse
Less specific: weight gain (>2 kg/week), weight loss (in advanced HF), tissue wasting (cachexia), cardiac murmur, peripheral oedema (ankle, sacral, scrotal), pulmonary crepitations, reduced air entry and dullness to percussion at lung bases (pleural effusion), tachycardia, irregular pulse, tachypnoea, cheyne stokes respiration, hepatomegaly, ascites, cold extremities, oliguria, narrow pulse pressure

[3] Left Atrial Enlargement defined by at least 1 of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm^2 or LA volume ≥55 mL or LA volume index ≥29 mL/m^2. Left Ventricular Hypertrophy defined by septal thickness or posterior wall thickness ≥1.1 cm

5.2 Exclusion criteria

1. Receiving therapy with an SGLT2 inhibitor within 4 weeks prior to randomisation or previous intolerance to an SGLT2 inhibitor.
2. Type 1 diabetes mellitus (T1D).
3. eGFR <25 mL/min/1.73 m^2 (CKD-EPI formula) at Visit 1.
4. Systolic blood pressure (BP) <95 mmHg on 2 consecutive measurements at 5-minute intervals, at Visit 1 or at Visit 2.
5. Systolic BP≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments, on 2 consecutive measurements at 5-minute intervals, at Visit 1 or at Visit 2.
6. MI, unstable angina, coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), ablation of atrial flutter/fibrillation, valve repair/replacement within 12 weeks prior to enrolment. Before enrolment, these patients must have their qualifying echocardiography and/or cardiac MRI examination at least 12 weeks after the event.
7. Planned coronary revascularization, ablation of atrial flutter/fibrillation and valve repair/replacement.
8. Stroke or transient ischemic attack (TIA) within 12 weeks prior to enrolment.
9. Probable alternative or concomitant diagnoses which in the opinion of the investigator could account for the patient's HF symptoms and signs (e.g. anaemia, hypothyroidism).
10. Body mass index >50 kg/m^2.
11. Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalisation for exacerbation of COPD requiring ventilatory assist within 12 months prior to enrolment).
12. Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronisation therapy.
13. HF due to any of the following: known infiltrative cardiomyopathy (e.g. amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), or uncorrected primary valvular disease.

14. A life expectancy of less than 2 years due to any non-cardiovascular condition, based on investigator's clinical judgement.
15. 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.
16. Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin).
17. Acute or chronic liver disease with severe impairment of liver function (e.g., ascites, oesophageal varices, coagulopathy).
18. Women of child-bearing potential (i.e. those who are not chemically or surgically sterilised or post-menopausal) not willing to use a medically accepted method of contraception considered reliable in the judgment of the investigator OR who have a positive pregnancy test at randomisation OR who are breast-feeding.
19. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site).
20. Previous randomisation in the present study.
21. Participation in another clinical study with an IP or device during the last month prior to enrolment.

5.3 Lifestyle restrictions (not applicable)

5.4 Screen failures

Enrolled patients who are found not eligible (i.e. not meeting all the inclusion criteria or fulfilling any of the exclusion criteria) must not be randomised or initiated on treatment.

Screen failures are defined as patients who signed the informed consent form to participate in the study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria (reason for screen failure), and any serious adverse event (SAE).

Screen failures may be re-enrolled one time during the study if the Investigator considers that the patient may be eligible for participation in this study at another time point. Re-enrolled patients should be assigned the same enrolment code as for the initial enrolment. All enrolment assessments and procedures, including signing the informed consent form, should be performed again.

5.5 Procedures for handling of randomized not eligible patients

If a patient is randomised and later found not eligible, the Investigator should immediately inform the AstraZeneca representative, who will report the protocol deviation to the AstraZeneca Study Physician.

Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. Regardless of whether study treatment is discontinued or not, the patient should continue his/her participation in the study for follow- up of endpoints and other protocol-defined study procedures until the end of the study. Consistent with the intention-to-treat principle, all randomised patients are included in the efficacy analysis according to randomised treatment assignment. The AstraZeneca Study Physician must ensure that the protocol deviation and the rationale for the decision to discontinue or continue study treatment are appropriately documented.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to dapagliflozin or matching placebo.

6.1 Treatments administered

Table 4 Study Treatments

	Dapagliflozin	Placebo
Investigational Product name	Dapagliflozin 10 mg	Matching placebo 10 mg
Dosage formulation	Green, diamond shaped, film coated tablets 10 mg	Green, diamond shaped, film coated tablets 10 mg placebo
Route of administration	Oral	Oral
Dosing instructions	Once daily	Once daily
Packaging and labeling	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements	Investigational Product will be provided in bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements
Provider	AstraZeneca	AstraZeneca

The tablets contain lactose, in quantities not likely to cause discomfort in lactose-intolerant individuals.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

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

Only patients randomised in the study may receive IP and only authorised site staff may supply or administer IP. The administration of all investigational products should be recorded in the appropriate sections of the eCRF.

The Investigator is responsible for IP accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

The investigator will retain the returned IP until the AZ representative or delegate collects it, along with any IP 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 IP is destroyed. The AZ representative or delegate will advise on the appropriate method for destruction of unused IP.

6.3 Measures to minimise bias: randomisation and blinding

All patients will be centrally assigned to randomised IP using an interactive voice/web response system (IxRS). Randomisation to IP will be performed in balanced blocks to ensure approximate balance between the treatment groups (1:1). The randomisation codes will be computer generated and loaded into the IxRS database. Before the study is initiated, the telephone number and call-in directions for the IxRS and/or the log-in information and directions for the IxRS will be provided to each site.

If a randomised patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn randomised patients will be included in the intention to treat analysis.

The IxRS will provide the Investigator with the kit identification number to be allocated to the patient at each dispensing visit. At all visits where IP is dispensed, site personnel will do a kit verification in IxRS before providing the IP bottle to the patient. Routines for this will be described in the IxRS user manual that will be provided to each centre.

The blinding of treatment is ensured by using a double-blind technique. 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 randomisation code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator is to document and report the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff.

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. Randomisation 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.

6.3.1 Stratification and capping

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

6.3.1.1 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. Stratification on T2D at the time of randomisation is based on:

- Established diagnosis of T2D

OR

- HbA1c ≥6.5% (48 mmol/mol) shown at central laboratory test at enrolment (Visit 1)

6.3.1.2 Capping

The intent is to enrol a typical cross-section of patients with HFpEF 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, subacute subgroup (i.e. randomised in- hospital or within 30 days from discharge) and atrial fibrillation status at Visit 1 may be capped in IxRS to avoid over- or under-representation of these patient subgroups.

6.4 Treatment compliance

The administration of all IP should be recorded in the appropriate sections of the eCRF. Any change from the dosing schedule should be recorded in the eCRF.

Patients will be asked to return all unused IP and empty packages to the clinic at the site visit except Visit 3. At each visit, any patient found to be non-compliant will be counselled on the importance of taking their IP as prescribed. The investigator or delegate will enter the number of returned tablets in the eCRF.

The Investigational Product Storage Manager is responsible for managing IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.5 Concomitant therapy

All patients should be treated according to regional standard of care of HFpEF and existing comorbidities (including treatment of hypertension, ischemic heart disease, atrial fibrillation, diabetes, hyperlipidaemia). Background medications should be part of clinical practice and will not be provided by the Sponsor.

6.5.1 Prohibited medication

Concomitant treatment (i.e., treatment in combination with IP) with open label SGLT2 inhibitors e.g., dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and fix dose combinations containing these drugs should not be used. 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. If treatment with an SGLT2 inhibitor alone or in combination is deemed essential, IP must be discontinued before that treatment is started.

6.5.2 Recording of concomitant treatment

Recording of relevant concomitant medications in the eCRF will be made according to the schedule of activities (Table 1). These include medications for cardiovascular conditions as well as diabetes mellitus.

6.5.3 Heart failure background standard of care

The patients should be on background standard of care therapies for patients with HFpEF according to local guidelines, including diuretics when needed to control symptoms and volume overload and adequate treatment of co-morbidities such as hypertension and ischaemic heart disease.

6.5.4 Anti-diabetes treatment

6.5.4.1 Background

More than 40% of patients with established HF are estimated to have T2D (Kristensen et al 2016). Therefore, it is expected that a large proportion of patients will have an established T2D diagnosis when included in this study and that some patients will develop T2D during the course of the study. Treatment of diabetes should follow established guidelines, such as 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).

6.5.4.2 Treatment of patients with established diagnosis of type 2 diabetes

Diabetes medications at baseline and during the study will be recorded in the eCRF. Patients with T2D at randomisation will continue their T2D treatment. SGLT2-inhibitors should be avoided (see Section 6.5.1). Patients treated with insulin or insulin secretagogues have a higher risk of experiencing hypoglycaemic events compared with those treated with other antidiabetic agents. If needed, T2D treatments may be adjusted at the discretion of the Investigator or diabetes health care provider.

6.5.5 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.

6.6 Dose modification (not applicable)

6.7 Treatment after the end of the study

The patients will stop taking IP at the study closure visit (SCV). Remaining IP will be collected at that time. Post-study treatment will not be provided by the Sponsor. Patients should receive standard of care therapy after the SCV, at the discretion of the Investigator.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Discontinuation from study treatment is NOT the same thing as a withdrawal from the study. If the patient temporarily or permanently discontinues IP, the patient should remain in the study and it is important that the scheduled study visits and data collection continue according to the study protocol until study closure.

Patients may be discontinued from IP in the following situations:

- Contraindication to further dosing with IP, in the opinion of the Investigator, such as Adverse event or other safety reasons.
- Severe non-compliance with the study protocol.
- Diabetic ketoacidosis (DKA). Consider temporarily interrupting IP if DKA is suspected. If DKA is confirmed, IP should be discontinued permanently.
- Positive pregnancy test (discontinue IP and notify Sponsor representative).
- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.

See the Table 1 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation

Every attempt should be made to maintain patients on IP during the course of the study. If IP has been interrupted, it should be re-introduced as soon as, in the opinion of the Investigator, the patient's condition is stable.

7.1.1.1 Unexpected acute declines in eGFR

If an unexpected, acute decline in kidney function is observed, the patient should be evaluated and temporary interruption of IP should be considered. 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.

7.1.1.2 Volume depletion/hypotension

Patients with clinically relevant symptoms/signs of suspected volume depletion and/or hypotension, should in addition to considering temporary interruption of IP have their regular medication reviewed, and consideration given to reducing the dose of, or stopping concomitant medications, as assessed on an individual basis, including diuretics and drugs that lower blood pressure. The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in light of the patient's symptoms and signs.

7.1.1.3 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.

7.1.2 Procedures for discontinuation of study treatment

Investigators should instruct their patients to contact the site before or at the time IP is stopped. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. Generally, AEs, SAEs, and potential endpoint events should not lead to IP discontinuation, unless there is a clear clinical rationale to do so.

The date of last intake of IP should be documented in the eCRF. All IP should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing IP should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of IP, for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn from the study.

Restart of randomised IP is always encouraged. 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.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and it is not possible for the site to get contact with the patient. To optimise the chance of getting in contact with the patient during the study, Investigators should record as much contact information as possible at the start of the study including home phone, mobile phone, holiday home phone, family member phone numbers, email address, and social media contact details.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed potentially lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by, e.g. repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Information regarding vital status should always be collected if possible.

7.3 Withdrawal from the study

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 has received appropriate information about and does not agree to any kind of further assessments or contact, including modified follow up options (see Section 7.1.2). 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 from the study 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. If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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, in compliance with local privacy laws/practices.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (see Section 1.1).

An Electronic Data Capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g. LVEF assessment) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1 Enrolment Period

8.1.1 Visit 1, Enrolment (Day -21 to Day -1)

Enrolment of hospitalized patients is allowed.

At enrolment the following assessments and procedures will be completed:

- The patient signs the ICF
  - Patients who agree to the optional sampling of blood for genetic research will provide their consent
- The investigator assesses patient's eligibility criteria and reviews concomitant medications, relevant medications will be recorded in the eCRF

- The patient will be enrolled and assigned an E-code in IxRS assuming inclusion/exclusion criteria are met
- Demography and relevant medical history (including prior cardiac imaging assessments) will be recorded
- A physical examination will be conducted
- NYHA Functional Classification will be evaluated and recorded
- 12-lead ECG will be recorded
- Vital signs (BP, pulse), height and weight will be assessed and recorded
- Blood samples will be taken for NT-proBNP, creatinine (for calculation of eGFR) and HbA1c assessment (central laboratory)

8.2 Treatment period

8.2.1 Visit 2, Randomisation (Day 1)

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

Randomisation of hospitalized patients is allowed.

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

- Medical history (including cardiac imaging assessments) will be re-assessed
- A physical examination will be conducted
- A pregnancy test for women of child-bearing potential will be done locally with a dipstick provided by central laboratory with result recorded in the medical record
- Vital signs (BP, pulse) will be assessed and recorded
- NYHA Functional Classification will be evaluated and recorded
- The investigator will re-assess the inclusion and exclusion criteria
- KCCQ, PGIS and EQ-5D-5L questionnaires will be completed
- Review of concomitant medication and recording of relevant medications
- If the patient has experienced any SAEs since last visit, this will be recorded in the eCRF

- Randomisation 1:1 ratio to IP (either dapagliflozin at 10 mg or placebo) will be done in IxRS
- 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
- Patients who have consented to sampling for genetic research, will provide a blood sample

8.2.2 Visit 3 (Day 30; ±7 days):

At Visit 3, the following assessments and procedures will be conducted:

- KCCQ and PGIS questionnaires will be completed
- NYHA Functional Classification will be evaluated and recorded
- Vital signs (BP, pulse) will be assessed and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events including COVID-19 testing results
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF
- Blood samples will be taken for creatinine (for calculation of eGFR) assessment (central laboratory)

8.2.3 Visit 4 (Day 120 ±7 days):

At Visit 4, the following assessments and procedures will be conducted:

- KCCQ and PGIS questionnaires will be completed
- NYHA Functional Classification will be evaluated and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events including COVID-19 testing results

- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.
- Blood samples will be taken for creatinine (for calculation of eGFR) assessment (central laboratory)
- IP will be dispensed via IxRS to the patient. Drug accountability of the returned IP will be checked. The patient will be instructed to take the IP in accordance with protocol and without interruptions

8.2.4 Visit 5 (Day 240 ±7 days)

At Visit 5, the following assessments and procedures will be conducted:

- KCCQ, PGIS and EQ-5D-5L questionnaires will be completed
- NYHA Functional Classification will be evaluated and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events including COVID-19 testing results
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.
- IP will be dispensed via IxRS to the patient. Drug accountability of the returned IP will be checked. The patient will be instructed to take the IP in accordance with protocol and without interruptions.

8.2.5 Visit 6 (Day 360 ±7 days)

At Visit 6, the following assessments and procedures will be conducted:

- Vital signs (BP, pulse), and weight will be assessed and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events including COVID-19 testing results
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.

- IP will be dispensed via IxRS to the patient. Drug accountability of the returned IP will be checked. The patient will be instructed to take the IP in accordance with protocol and without interruptions.
- Blood samples will be taken for creatinine (for calculation of eGFR) assessment (central laboratory)

8.2.6 Visit 7 and onwards (Day 480 and every 120 days ±14 days)

At visit 7 and subsequent visits, the following assessments and procedures will be conducted:

- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events including COVID-19 testing results
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF.
- IP will be dispensed via IxRS to the patient. Drug accountability of the returned IP will be checked. The patient will be instructed to take the IP in accordance with protocol and without interruptions.
- Starting from Visit 6, vital signs (BP, pulse), and weight assessment as well as blood samples collection for creatinine (for calculation of eGFR) will be repeated every 12 months - on Visit 6, Visit 9 and Visit 12.

8.2.7 Premature Treatment Discontinuation Visit

Patients who prematurely and permanently discontinue treatment with IP should return for a premature treatment discontinuation visit (PTDV), which will be done as soon as possible after last dose of IP. The following assessments and procedures will be conducted:

- KCCQ, PGIS and EQ-5D-5L questionnaire will be completed
- NYHA Functional Classification will be evaluated
- Vital signs (BP, pulse) and weight will be assessed and recorded
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures

- Review of potential efficacy and safety events including COVID-19 testing results
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF
- Drug accountability of the returned IP will be checked

Patients who discontinue treatment prematurely should attend all study visits according to plan, including the study closure visit (SCV). Patients may re-start treatments if assessed as appropriate by the Investigator. For further details regarding discontinuations from IP, please see Section 7.1.

8.2.8 Study Closure Visit

A primary analysis censoring date (PACD) will be declared based on the rate of accrued endpoints. A study closure visit (SCV) will be scheduled within 6 weeks of the PACD. All patients (including any patients who have discontinued treatment with IP) should return for this visit.

The patient will stop taking IP at the SCV. Remaining IP will be collected at that time and drug accountability will be checked. The following assessments and procedures will be conducted:

- KCCQ, PGIS and EQ-5D-5L questionnaire will be completed
- NYHA Functional Classification will be evaluated
- A physical examination will be conducted
- Vital signs (BP, pulse) and weight will be assessed and recorded.
- Review and updating of concomitant medication and recording of relevant medications
- Review and recording of any cardiac and HF related procedures
- Review of potential efficacy and safety events including COVID-19 testing results
- If the patient has experienced any potential endpoints, SAEs, DAEs and/or amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs since the last visit, this will be recorded in the eCRF
- Drug accountability of the returned IP will be checked

8.2.9 Unscheduled visits

An unscheduled on-site or telephone visit may occur in-between scheduled on-site visits (for example assessment of potential endpoint events or safety events).

8.3 Efficacy assessments

8.3.1 Efficacy event capture

Efficacy events (i.e. death, hospitalisation or urgent visits for HF) will be collected by site personnel according to the study visit schedule. All potential efficacy events should be recorded as an AE and on additional event modules in the eCRF. If the potential efficacy event fulfils SAE criteria (see Appendix B 2) the site is to record and report these events to the sponsor or designee within timelines described in Section 8.6.

NYHA classification will be done by the Investigators and recorded in the eCRF. PROs will be collected for all patients throughout the study period via a hand-held electronic device. All-cause hospitalisations will be derived from SAE reports.

8.3.2 Efficacy event adjudication

A Clinical Events Adjudication (CEA) Committee will be established for this trial and adjudicate primary efficacy events in accordance with adjudication criteria detailed in the CEA charter.

Events to be adjudicated include components of the primary efficacy endpoint: deaths, hospitalisation for HF, and urgent HF visits. All deaths will be adjudicated to determine if they are CV or non-CV deaths. All adjudication will be done on an ongoing basis throughout the trial.

8.3.3 Clinical Outcome Assessments (COA)

A COA is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. Patient Reported Outcomes (PROs) is one of the types of COAs. A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of anyone else. PROs have become a significant endpoint when evaluating benefit/risk of treatments in clinical trials. The following PROs will be collected: KCCQ, PGIS and EQ-5D-5L (see Appendix I, Appendix K, Appendix L). PROs will be collected for all patients throughout the study period via a hand-held electronic device. See study of assessment (See Table1) for the timing of collection. The ePRO devices should be administered prior to first dose at visit 2/randomisation. Site staff should stress that the information is confidential.

8.3.3.1 KCCQ

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item, self-administered disease specific instrument and has shown to be a valid, reliable and responsive measure for patients with HF (Greene et al 2018, Spertus et al 2005). The KCCQ was developed to independently measure the patient's perception of their health status, which includes heart failure-related symptoms (frequency, severity and recent change), impact on physical and social function, self- efficacy and knowledge, and how their heart failure impacts their quality of life (QOL). Scores are transformed to a range of 0-100. Higher scores represent a better outcome.

The KCCQ tool quantifies the following six (6) distinct domains and two (2) summary scores:

- KCCQ Symptom Domain quantifies the frequency and burden of clinical symptoms in heart failure, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea and patients' edema/swelling. An overall symptom score is generally used in analyses; subscale scores for both frequency and severity are also available. The total symptom Score incorporates the symptom domains into a single score

- KCCQ Physical Function Domain measures the limitations patients experience, due to their heart failure symptoms, in performing routine activities. Activities are common, gender-neutral, and generalizable across cultures, while also capturing a range of exertional requirements

- KCCQ Quality of Life Domain is designed to reflect patients' assessment of their quality of life, given the current status of their heart failure

- KCCQ Social Limitation Domain quantifies the extent to which heart failure symptoms impair patients' ability to interact in a number of gender-neutral social activities

- KCCQ Self-efficacy Domain quantifies patients' perceptions of how to prevent heart failure exacerbations and manage complications when they arise. This scale is not included in the summary scores

- KCCQ Symptom Stability Domain measures recent changes in patients' symptoms; their shortness of breath, fatigue or swelling. It compares patients frequency of heart failure symptoms at the time of completing the KCCQ with their frequency 2 weeks ago. As a measure of change, it is most interpretable as a baseline assessment of the stability of patients' symptoms at the start of a study and shortly thereafter, as a measure of the acute response to treatment. This domain is not included in the summary scores.

- Clinical Summary Score includes total symptom and physical function scores to correspond with NYHA Classification

- Overall Summary Score includes the total symptom, physical function, social limitations and quality of life scores

8.3.3.2 Patient Global Impression of Severity (PGIS)

The PGIS item is included to assess how a patient perceives his/her overall current severity of heart failure symptoms. Patients will choose from response options from "no symptoms" to "very severe".

8.3.3.3 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.

8.3.3.4 Administration of electronic PROs

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. A key aspect of study success is to have high PRO compliance. Therefore, it is essential to follow SoA and that sites make sure the device is charged and fully functional at all times in order to minimize missing data.

It is important that the site staff explains the value and relevance of PRO data: to hear directly from patients how they feel. The following best practice guidelines should be followed:

- 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 (except the Visit 2: eligibility confirmation before the KCCQ)
- Before being seen by the investigator
- PRO questionnaires must be completed by the patient in private
- The appointed site personnel should also stress that the information is confidential. Therefore, if the patient has any medical problems, he or she should discuss them with the doctor or research nurse separately from the ePRO assessment
- 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 a site is affected by COVID-19 pandemic and on-site visits are not possible, phone collection of ePRO is an alternative solution to maintain continuity of the assessments. The details of the procedure will be provided in a separate instruction.

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.

8.4 Safety assessment

Planned time points for all safety assessments are provided in the schedule of activities (Table 1).

8.4.1 Physical examinations

A 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.

The assessment dates will be recorded in the eCRF.

8.4.2 Vital Signs

- Pulse and BP will be measured twice at all applicable visits, and all measurements will be recorded in the eCRF.
- The measurements should be done before any blood sampling. The measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- The measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

8.4.3 Electrocardiogram

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 baseline (Visit 1) after the patient has been lying down to rest for at least 5 minutes, to confirm presence or absence of atrial fibrillation/flutter at enrolment. Heart rate and heart rhythm will be reported in the eCRF. The baseline ECG should be stored and be made available upon request for adjudication purposes

8.4.4 Safety laboratory assessments

Serum creatinine will be collected for calculation of eGFR using CKD-EPI equation (Levey et al 2009).

8.4.5 Other safety assessments

If COVID-19 testing was done, the type of test and result (positive/negative) should be recorded in the eCRF.

8.4.6 Other clinical assessments

8.4.6.1 Body weight and height

The patient's body weight will be measured with light clothing and no shoes. If the patient has a prosthetic limb, this should be consistently 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.

8.5 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of a SAEs and DAEs, amputation and events potentially placing the patient at risk for a lower limb amputation (preceding events). For information on how to follow-up AEs see Section 8.5.3.

8.5.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting SAEs or DAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

Safety information on SAEs and DAEs, amputations, adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs will be collected and entered into eCRFs by site personnel according to the study visit schedule.

If the potential efficacy event fulfils SAE criteria (see Appendix B 2) the site is to record and report these events to the Sponsor or designee within timelines described in Section 8.6.1.

8.5.1.1 Adverse events (AEs) leading to amputation and potential risk factor AEs for amputations affecting lower limbs ("preceding events")

To ensure that data on amputations is systematically collected, amputations and underlying conditions relevant to amputation 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 to amputation, non-serious and serious events potentially placing the patient at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as AE/SAE whether or not an amputation has taken place. The lower limb amputation "preceding events" of interest include diabetic foot related conditions, vascular, volume depletion, wounds/injury/trauma, infection and neuropathy. If any of these or other potentially relevant events have occurred, relevant information must be provided (this will be collected on a dedicated eCRF page - for details see eCRF instruction)".

8.5.1.2 Capture of DKA events

For SAEs or DAEs reported by the Investigator as Diabetic Ketoacidosis (DKA - see definition below) additional information will be recorded on specific eCRF pages in addition to the AE/SAE form. All potential events of DKA will be submitted to an independent DKA Adjudication Committee, see Section 8.5.1.2.2)

8.5.1.2.1 DKA definition

A diagnosis of Diabetic Ketoacidosis should only be made in a clinical setting consistent with DKA (based on patient history, symptoms, and physical exam) and in the absence of more likely alternative diagnoses and causes of acidosis (such as lactic acidosis). The following biochemical data should support diagnosis:

- Ketonaemia ≥3.0 mmol/L and/or significant ketonuria (more than 2+ on standard urine sticks)
- At least one of the following criteria suggesting high anion gap metabolic acidosis:
  - Arterial or Venous pH ≤7.3
  - Serum bicarbonate ≤18 mEq/L
  - Anion gap [Na – (Cl + HCO3)] >10

8.5.1.2.2 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.

8.5.1.3 Capture of cardiac ischaemic events and stroke

For myocardial infarctions, unstable angina and stroke additional information will be recorded on specific eCRF pages in addition to the AE/SAE form.

The diagnosis of stroke, MI and unstable angina should be made according to standard clinical practice and align with the definition for stroke in the standardised definitions for endpoints (Hicks et al 2018) described in Appendix C.

8.5.1.4 Capture of Major hypoglycaemic events

A major hypoglycemic event is defined as an event that is characterized by altered mental and/or physical status, any symptoms of severe impairment in consciousness or behavior, that require external assistance of another person for treatment of hypoglycemia and recovery, to actively administer carbohydrates, glucagon, or take other corrective actions.
Plasma glucose concentrations may not be available during a hypoglycaemic 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.

8.5.1.5 Capture of additional laboratory values

Any additional safety laboratory assessments during the study period, including creatinine, will be obtained per the Investigator's medical judgment in the course of standard care using local laboratories. Laboratory values would be recorded only on SAE eCRFs as part of narrative information, per the Investigator's judgment.

8.5.2 Time period and frequency for collecting AE and SAE information

Non-serious adverse events as defined per protocol will be collected from randomisation (Visit 2), throughout the treatment period until and including the patient's last visit (the study closure visit). Serious adverse events are recorded from the time of signing of informed consent form throughout the treatment period until and including the patient's last visit.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.5.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAE and events of amputation and potential preceding events will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

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.

8.5.4 Adverse event data collection

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 Investigational Product(s) (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

8.5.5 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 B to the Clinical Study Protocol.

8.5.6 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 they fulfil the criteria specified in Section 8.5.2. 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.

8.5.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated vital signs and laboratory values will be summarised in the clinical study report. Deterioration as compared with baseline in protocol-mandated 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 IP. If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE if they

fulfil any of the SAE criteria or are the reason for discontinuation of treatment of IP, and the associated vital sign will be considered as additional information.

8.5.8 Disease-under study (DUS) (not applicable)

8.5.9 Disease progression (not applicable)

8.6 Safety reporting and medical management

8.6.1 Reporting of serious adverse events

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 adverse events 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 EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.6.1.1 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 8.6.1).

In addition, fatal AEs and potential HF endpoints will be centrally adjudicated by an independent CEA committee (see Section 8.3.1 and 8.3.2). 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 8.6.1) 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).

8.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study patient has received any IP. If a pregnancy is reported, the Investigator should inform the sponsor within 24 hours of learning of the pregnancy. Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.6.2.1 Maternal exposure

Women of childbearing potential who are not using contraception as defined in Section 5.2; exclusion criterion number 18 are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

Dapagliflozin must not be used in the second and third trimesters of pregnancy. In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

There are no adequate and well-controlled studies of dapagliflozin in pregnant women. When pregnancy is detected, investigational product(s) should be discontinued.

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

If an overdose on an AstraZeneca IP 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 8.5.2. For other overdoses, reporting must occur within 30 days.

8.7 Pharmacokinetics (not applicable)

8.8 Pharmacodynamics (not applicable)

8.9 Optional exploratory genetics

Approximately 6 mL blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D.

8.10 Biomarkers (not applicable)

8.11 Health Economics (not applicable)

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

For the primary and secondary endpoints, the following hypothesis will be tested at the 4.980 % 2-sided level:

H0: HR [dapagliflozin:placebo] =1

versus

H1: HR [dapagliflozin:placebo] ≠1

9.2 Sample size determination

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo added to standard of care in reducing the composite of CV death and heart failure events (hospitalisation for HF or urgent HF visit). Two hypotheses will be tested simultaneously (i.e., dual primary analyses) for the primary objective: (1) in the full population and in (2) an LVEF <60% subpopulation, with alpha allocated to each test. Originally, assuming a true hazard ratio (HR) of 0.80 between dapagliflozin and placebo, using a two-sided alpha of 5%, 844 primary endpoint

events were targeted in order to provide a statistical power of 90% for the test of the primary composite endpoint. To allow testing for the dual primary analyses, alpha will be allocated to each test to ensure strong control of the overall type I error rate. The target number of patients with a primary endpoint has been increased to 1117 in order to provide adequate statistical power for each test. It is anticipated that at least 70% of the events (i.e., approximately 780 events) will be available for the LVEF <60% subpopulation. To illustrate, assuming a true HR of 0.80, a two-sided alpha of 2.4% allocated to the LVEF <60% subpopulation will result in a power of 80% to detect a treatment difference, whereas an alpha allocation of 1.5% to the full population will result in 90% power. The final alpha split for the dual primary analyses will be specified in the SAP prior to the planned interim analysis. This is based on an overall 1:1 allocation between dapagliflozin and placebo.

The HR 0.80 was originally chosen as a conservative assumption based on the observed HR 0.72 (95% confidence interval 0.50-1.04) for the composite of HF hospitalisation and CV death in patients with HF at baseline in the EMPA- REG OUTCOME trial (Fitchett et al 2016) and HR 0.61 (0.46-0.80) for patients with history of HF in the CANVAS program (Rådholm et al 2018) considering that these were post-hoc analyses in subgroups with limited documentation of baseline HF diagnosis, not characterised by ejection fraction.

The event rate assumptions are based on sub analyses of the TOPCAT and I-PRESERVE studies by geographic region, NT-proBNP levels, prior hospitalisation for HF, and T2D status (Pfeffer et al 2015, Kristensen et al 2015, Kristensen et al 2017). The original sample size calculation (~ 4700 randomized patients) built on the assumption of an annual event rate of 9% in the placebo group for the majority of prevalent HFpEF patients, importantly all with NT -proBNP ≥300 pg/ml by inclusion criterion. Additionally, a subgroup of patients due to be discharged or recently discharged from a HF hospitalisation (here denoted 'subacute' patients) with a higher event rate is planned to be included. Assuming 20% of patients from the subacute category with an annual event rate of 24% during the first year and 9% thereafter for the remainder of the study, the original sample size of 4700 patients was estimated to provide the required number of 844 patients with a primary event during a recruitment period of 18 months and a minimum follow-up period of 15 months.

Based on the ongoing blinded monitoring of event accrual (including the percentage of patients from the subacute category), the sample size is increased from original 4700 to approximately 6100 randomised patients. Accordingly, the recruitment period is anticipated to increase from the original 18 months to 26 months. Recruitment might be marginally prolonged in a few countries to meet local targets. The study is event driven and the number of patients or duration may further change.

With the same event rate assumptions as above, assuming 11% of patients from the subacute category, approximately 6100 patients are estimated to provide the required number of 1117 patients with a primary event during an anticipated recruitment period of 26 months and a minimum follow-up period of 13.5 months (total study duration 39 months).

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.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Table 5 Population for analysis

Population	Description
Enrolled	All patients who sign the ICF
Full Analysis Set (FAS)	All patients who have been randomised to study treatment, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised investigational product assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the intention to treat analysis of primary and secondary variables. A subset of the full analysis set consisting of patients with baseline LVEF of <60% (or LVEF <60% subpopulation) will be analysed separately as part of the confirmatory statistical testing procedure.
Safety analysis set	All patients randomly assigned to Study treatment and who take at least 1 dose of investigational product. 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

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be developed prior to first patient randomised and any subsequent amendments will be documented, with final amendments finalised before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

9.4.1 Efficacy analyses

9.4.1.1 Analysis of the primary variable

The primary variable is the time from randomisation to first event included in the primary composite endpoint. Two hypotheses will be tested simultaneously (i.e., dual primary endpoint analyses): (1) in the full population and (2) in an LVEF <60% subpopulation, with alpha allocated to each test. The primary analysis will be based on the ITT principle using the FAS, including events occurring on or prior to the PACD, adjudicated by the CEA committee.

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. 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 analyse the time from randomisation to the first occurrence of each component of the primary composite endpoint. 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.

9.4.1.2 Analysis of the secondary variables

The outcome of all HF events (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. The rate ratio and its 95% confidence interval and corresponding two-sided p-value will be presented. This outcome will also be analysed for the LVEF <60% subpopulation within the multiple testing procedure as described in Section 9.2.

The analysis of change from baseline for KCCQ total symptom score at 8 months will be further detailed in the statistical analysis plan, e.g. with consideration of handling of patients who die. In addition to the secondary endpoint, total symptom score, the overall summary score, clinical summary score and domain scores will be analysed. A responder analysis will also be performed (more details presented in the SAP).

The analysis of the endpoints time from randomisation to CV death and time to all-cause mortality will be analysed in the similar manner as the primary variable.

9.4.1.3 Subgroup analysis

Subgroup variables for the primary efficacy endpoint include demography, baseline disease characteristics, baseline concomitant medications and others. Cox proportional hazard model stratified for T2D with factors for treatment group, the subgroup variable and the interaction between treatment and subgroup will be used to examine treatment effects within relevant subgroups separately. A test of interaction between randomised treatment group and the subgroup variable will be performed in each Cox model. 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.

9.4.1.4 Sensitivity analysis

Details of the sensitivity analysis for the primary and secondary endpoints will be provided in the SAP.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety analysis set. The number and percent of patients with SAEs, DAEs, amputations, and potential preceding events for lower limb amputations will be summarised by treatment group, and by system organ class and preferred term.

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

9.4.3 Methods for multiplicity control

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilised. The Type I error will be controlled at an overall two-sided 5% level for multiplicity across primary and secondary endpoints and in consideration of the planned interim analysis. With one interim analysis at 67% of events (see Section 9.5) the two-sided significance level in final analysis, α, will be 4.980%. Statistical significance will be assessed in two branches in a pre-specified order of the endpoints and populations which is further described in the SAP. The significance level α, will be split for the two primary analyses, denoted α_1 and α_2. If either of the tests of the primary endpoint in the full study population and for LVEF <60% subpopulation is significant at respective levels α_1 and α_2, the next hypothesis in the respective branch sequence will be tested at the same significance level. The exact split of alpha will be documented in an updated SAP before the interim analysis. If all hypotheses in one arm are rejected, the alpha will be recycled to the other branch.

9.5 Interim analyses

An interim analysis is planned to be performed including approximately 67% of the target number of patients with adjudicated primary endpoint events (approximately 748 events). There will in principle be one planned interim analysis for efficacy, with the possibility of the DMC to conduct 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 of interim analyses. The interim analysis will assess superiority of dapagliflozin to placebo. The interim analysis will have a nominal two-sided alpha level of 0.2%. At the interim analysis, the primary composite endpoint will be tested in the full study population 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 in the full study population at a two-sided level of 0.2%. 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.

In the initial version of the protocol, there was a planned futility analysis to be performed at the time of interim analysis. This futility analysis was removed, since formal testing was updated to

include both the LVEF <60% subpopulation and full study population, and that this potentially creates complex scenarios related to futility and benefit in one, other or both populations.

9.5.1 Data monitoring committee (DMC)

An independent data monitoring committee (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. 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 charter will be prepared to detail precise roles and responsibilities and procedures of the DMC.

10. REFERENCES

Ambrosy et al 2014
Ambrosy AP, Gheorghiade M, Chioncel O, Mentz RJ, Butler J. Global perspectives in hospitalised heart failure: regional and ethnic variation in patient characteristics, management, and outcomes. Curr Heart Fail Rep 2014 Dec;11(4):416-27.

Borlaug and Paulus 2011
Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 2011;32:670-9.

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

Butler et al 2014
Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC Heart Fail 2014 Apr;2(2):97-112.

Cherney et al 2014
Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, et al. The effect of the empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014;13:28.

Chilton et al 2015
Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metabo 2015;17:1180-93.

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 Feb 15;171(3):368-76.

EMA Guidance 2016
EMA 2016; Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (draft), Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/392958/2015.

FDA Draft Guidance for Industry 2016
Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices. Draft Guidance for Industry and Food and Drug Administration Staff. 16 September 2016.

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;14;37(19):1526-34.

Greene et al 2018
Greene SJ, Mentz RJ, Felker GM. Outpatient Worsening Heart Failure as a Target for Therapy: A Review. JAMA Cardiol. 2018 Jan 31. doi:10.1001/jamacardio.2017.5250. [Epub ahead of print] PubMed PMID: 29387880.

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 Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC August 20, 2014.

Hicks et al 2018
Hicks KA, Mahaffey KW, Mehran R, Nissen SE, et alCardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021–34

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). Diabetes Care. 2012 Jun;35(6):1364-79.

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

Iwaz et al 2016
Iwaz JA, Le E, Aramin H, Romero D, Iqbal N, Kawahara M, et al. New targets in the drug treatment of heart failure. Drugs 2016;79:187-201.

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

Kosiborod et al 2017a
Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al, on behalf of the CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study. Circulation 2017 May 18. pii: CIRCULATIONAHA.117.029190. doi: 10.1161/CIRCULATIONAHA.117.029190.

Kosiborod et al 2017b

Kosiborod M, Gause-Nilsson I, J Xu J, Sonesson C, Johnsson E. Efficacy and safety of and dapagliflozin in patients with type 2 diabetes mellitus concomitant heart failure. J Diabetes Complications 2017; 31 (7):1215-21.

Kristensen et al 2015
Kristensen SL, Jhund PS, Køber L, McKelvie RS, Zile MR, Anand IS, et al. Relative importance of history of heart failure hospitalisation and N-terminal Pro–B-type natriuretic peptide level as predictors of outcomes in patients With heart failure and preserved ejection fraction. JACC Heart Fail 2015 Jun;3(6):478-86.

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.

Kristensen et al 2017
Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D1, Win S, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation. 201721;135(8):724-35.

Lam et al 2011
Lam CSP, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. European Journal of Heart Failure 2011; 13: 18–28.

Lam et al 2020
Lam CSP, Voors AA, Ponikowski P, McMurray JJV, Solomon SD. Time to rename the middle child of heart failure: heart failure with mildly reduced ejection fraction. European Heart Journal 2020; 41:2353-55.

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.

Nauta et al 2017
Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CSP, Ponikowski P, Voors AA. What have we learned about heart failure with mid□range ejection fraction one year after its introduction? European Journal of Heart Failure 2017; 19(12): 1569-1573.

Neal et al 2017
Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al, for the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377: 644-657.

Oktay et al 2013
Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep 2013;10(4):401-10.

Okumura et al 2016
Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ; 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 Jun 7;133(23):2254-62. doi:
10.1161/CIRCULATIONAHA.115.020729. Epub 2016 Apr 20. PubMed PMID: 27143684.

Ott et al 2017
Ott C, Jumar A, Striepe K, Friedrich S, Karg MV, Bramlage P, et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. Cardiovasc Diabetol 2017;16:26.

Pfeffer et al 2015
Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation. 2015;131:34-42.

Rådholm et al 2018
Rådholm K, Figtree, Perkovic V, Solomon SD, Mahaffey KW, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation. 2018;137
https://doi.org/10.1161/CIRCULATIONAHA.118.034222

Shigiyama et al 2017
Shigiyama F, Kumashiro N, Miyagi M, Ikehara K, Kanda E, Uchino H, et al. Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. Cardiovasc Diabetol 2017;16:84. DOI 10.1186/s12933-017-0564-0.

Skali et al 2014
Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R, Kukin M, Lichstein E, McNitt S, Moss AJ, Pfeffer MA, Solomon SD. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. Eur J Heart Fail. 2014 May;16(5):560-5. doi: 10.1002/ejhf.71. Epub 2014 Feb 27. PubMed PMID: 24578164.

Solomon et al 2005

Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA; Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005 Dec 13;112(24):3738-44

Solomon et al 2019
Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Saraiva JFK, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, PARAGON-HF Investigators and Committees; Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. The New England Journal of Medicine 2019; 381:1609-1620.

Solomon et al 2020
Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, Rouleau JJ, Pfeffer MA, Desai A, Lund LH, Kober L, Anand I, Sweitzer N, Linssen G, Merkely B, Arango JL, Vinereanu D, Chen CH, Senni M, Sibulo A, Boytsov S, Shi V, Rizkala A, Lefkowitz M, McMurray JJV; Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation 2020; 141:352-361.

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.

Thygesen et al 2012
Thygesen Kristian, Alpert Joseph S., Jaffe Allan S., Simoons Maarten L, Chaitman ,White Harvey D. Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third Universal Definition of Myocardial Infarction. Global Heart Vol: 7 (4), 2012 Page: 275-295

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

Zannad et al 2014
Zannad F Garcia AA, Anker SD Armstrong PW Calvo G et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. Eur J Heart Failure 2013;15:1082–94.

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.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

A subject who is rescreened is required to sign another ICF.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study- related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

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 committee and DMC 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 regards 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 nonvoting members of the Sponsor, and will operate under an Executive Committee charter.

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.

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.

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.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre- existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event 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-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the subject 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 subject'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).

B 4 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 subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

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 subject or may require medical treatment 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 (e.g. neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 Appendix B 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 Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When assessing 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 subject 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.

B 8 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 investigational product that either causes harm to the participant or has the potential to cause harm to the participant.

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 participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant 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 participant
- 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 participant received the medication (excluding IxRS errors)
- Wrong drug administered to participant (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
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant 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.

Appendix C Cardiovascular related events

C 1 Myocardial Infarctions (MI)

MIs are not endpoints in this study but unstable angina and myocardial infarction should be recorded as SAEs if serious criteria are met and additional information be collected in specific eCRF. The diagnoses of unstable angina and MI should adhere to the standardised definitions for endpoints (Hicks et al 2018) described in Appendix C 2

C 2 Diagnosis of MI and Unstable Angina

Myocardial infarction (MI)

The diagnosis of an MI should be made according to standard clinical practice but is expected to align with the criteria from Third Universal Definition of MI, i.e. detection of a rise and/or fall of cardiac biomarkers such as troponin and at least one of the following: typical clinical symptoms, ischaemic ECG findings, imaging evidence of myocardial injury, or detection of an intracoronary thrombus by angiography or autopsy (Thygesen et al 2012).

The diagnosis should be made by, or in consultation with, a cardiologist. The findings supporting the diagnosis should be documented in the description of the SAE in the eCRF.

Unstable Angina (UA)

Unstable Angina (UA) is not an endpoint in this study but should be recorded as SAEs (and DAEs when appropriate). The diagnosis of an UA should be made according to standard clinical practice but is expected to align with the following definition:

The diagnosis of unstable angina will require ischemic chest pain (or equivalent) at rest ≥10 minutes in duration considered to be myocardial ischemia upon final diagnosis and prompting hospitalisation within 24 hours of the most recent symptoms, and without elevation in cardiac biomarkers of necrosis, and the presence of objective evidence of ischemia as defined by at least 1 of the following criteria:

1. New or worsening ST or T wave changes in ≥2 anatomically contiguous leads on a resting ECG (in the absence of LVH and LBBB):

a) transient (<20 minutes) ST elevation at the J point ≥ 0.2 mV in men (> 0.25 mV in men < 40 years old) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads, or

b) horizontal or down-sloping ST depression ≥ 0.10 mV, or

c) T-wave inversion ≥ 0.2 mV

2. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs.

3. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

C 3 Stroke

Stroke is not an endpoint in this study but should be recorded as SAEs if serious criteria are met, with additional information e.g. classification of stroke type (ischaemic, haemorrhagic, or undetermined) collected in a specific eCRF.

The diagnosis of stroke should be made according to standard clinical practice and align with the definition for stroke in the standardized definitions for endpoints (Hicks et al 2018) described in Appendix C 4 and be differentiated vs Transient Ischaemic Attack (TIA).

C 4 Definition of Stroke and Transient Ischemic Attack

The distinction between an Ischemic Stroke and a Transient Ischemic Attack is the presence of infarction. Persistence of symptoms ≥24 hours or until death[3] is an acceptable indicator of acute infarction in the absence of imaging evidence of infarction.

Transient Ischemic Attack
Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction.

Stroke
Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
Haemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with haemorrhagic transformation and not a haemorrhagic stroke.

B. Haemorrhagic Stroke

Haemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by non-traumatic intraparenchymal, intraventricular, or subarachnoid haemorrhage. NOTE: Subdural hematomas are intracranial haemorrhagic events and not strokes.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction but with insufficient information to allow categorization as either ischemic or haemorrhagic.

References:

Hicks KA et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 2018;71:1021–34 https://doi.org/10.1016/j.jacc.2017.12.048

Draft Definitions for CDISC August 20, 2014

Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MSV, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee J-M, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064-2089.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the subject´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on heart failure with preserved ejection fraction continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject decline to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and** Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:
Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research
The blood sample for genetic research will be obtained from the subjects at Visit 2. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples
The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely withdrawal from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Handling of Human Biological Samples

E 1 Chain of custody of biological samples

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

The Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

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 will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

E 2 Withdrawal of Informed Consent for donated biological samples

If a subject 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 the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

E 3 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 (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations 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 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 (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.ht m)

- **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 F Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law (not applicable)

Appendix G Medical device incidents: definition and procedures for recording, evaluating, follow-up, and reporting (not applicable)

Appendix H Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
BP	Blood Pressure
CEA	Clinical Event Adjudication
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CSA	Clinical study Agreement
CV	Cardiovascular
DAE	Adverse Event leading to discontinuation of investigational product
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDC	Electronic Data Capture
EHRs	Electronic Health Records
FAS	Full Analysis Set
GCP	Good Clinical Practice
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HR	Hazard Ratio
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.
IxRS	Interactive Voice/Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAE	Left Atrial Enlargement
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction

NYHA	New York Heart Association
PACD	Primary Analysis Censoring Date
PTDV	Premature Treatment Discontinuation Visit
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCV	Study Closure Visit
SoA	Schedule of Activities
T2D	Type 2 Diabetes Mellitus

Appendix I New York Heart Association (NYHA) Functional Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (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 J The KC Cardiomyopathy Questionnaire

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 stopping	❑	❑	❑	❑	❑	❑
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 everyday**	**1 – 2 times per week**	**Less than once a week**	**Never over the past 2 weeks**
❑	❑	❑	❑	❑	❑	❑

8. Over the past 2 weeks, 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 past 2 weeks, 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 per 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 past 2 weeks, how much has your **heart failure** limited your 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 right now, 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 weeks. Please 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 relationships with loved ones	❑	❑	❑	❑	❑	❑

 Original US English

Appendix K EQ-5D-5L Questionnaire

Health Questionnaire

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

MOBILITY

I have no problems walking ❑

I have slight problems walking ❑

I have moderate problems walking ❑

I have severe problems walking ❑

I am unable to walk ❑

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 ❑

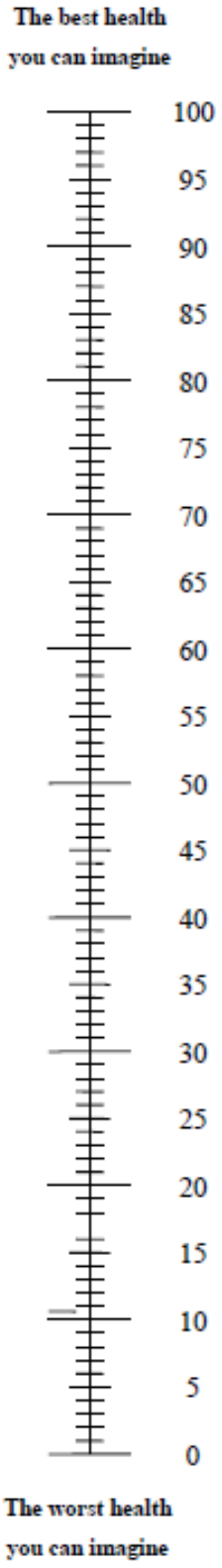
I am moderately anxious or depressed ❑

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 best health you can imagine.
  0 means the worst 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 = ☐



Appendix L Patient Global Impression of Severity for Heart Failure Symptoms

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

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d169cc00001-csp-v4		
Document Title:	D169CC00001 Clinical Study Protocol version 4	
Document ID:	Doc ID-003827083	
Version Label:	6.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
13-Nov-2020 13:23 UTC	[redacted]	Content Approval
16-Nov-2020 16:15 UTC	[redacted]	Content Approval
13-Nov-2020 07:36 UTC	[redacted]	Content Approval
16-Nov-2020 08:56 UTC	[redacted]	Content Approval
13-Nov-2020 08:29 UTC	[redacted]	Qualified Person Approval

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