Clinical Study Protocol

Drug Substance	Dapagliflozin
Study Code	D169EC00001
Version	3.0
Date	4 March 2020

An International, Multicentre, Parallel-group, Randomised, Double-blind, Placebo-controlled, Phase III Study Evaluating the effect of Dapagliflozin on Exercise Capacity in Heart Failure Patients with Preserved Ejection Fraction (HFpEF)

Short Title: DETERMINE-preserved – Dapagliflozin EffecT on ExeRcise capacity using a 6-MINutE walk test in patients with heart failure with preserved ejection fraction

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s): EudraCT 2018-003441-42

VERSION HISTORY

Version 1.0 15 January 2019	Initial creation
Version 2.0 7 November 2019	Section 1.1 (Schedule of activities): Table 1 was changed to reflect changes in the CSP text. Section 1.2 (Synopsis): Updated to reflect changes in the CSP text, including the study period changed due to prolonged recruitment, and the exact aligning of the endpoint wording with the one in Section 3. Section 3 (OBJECTIVES AND ENDPOINTS): Primary and key secondary objectives were combined into dual primary objectives and sample size was increased to 500, to increase the power in evaluating the effect of dapagliflozin on KCCQ in HFpEF subjects. Exploratory objectives were reordered and rephrased. Section 4.1 (Overall design): The target of having approximately 400 patients randomized was changed to 500. Section 4.2 (Scientific rationale for the study): Explanation of using pre-specified 5-point threshold in KCCQ was added. Section 5.1 and 5.2 (Inclusion criteria and Exclusion criteria) were clarified. Section 6.3.1.2 (Capping) was updated to allow it on a level lower than the whole study. Section 7.1.1.1 (Unexpected acute declines in eGFR): a clarification note added. Section 7.4 (Discontinuation of the study): Reasons for the early closure of the study site were added as per more recent protocol template. Section 8 (STUDY ASSESSMENT AND PROCEDURES): Additional information was added to Visit 4 description. This visit is now allowed to be performed in-clinic.

	Also, subsections revised for consistency with the changes introduced in the objectives and sample size. Section 9 (STATISTICAL CONSIDERATIONS) revised for consistency with the changes introduced in the objectives and sample size. General: minor editing corrections for consistency in minor sections.
Version 3.0 4 March 2020	The main purpose of this amendment was to add a primary objective to the study (ie, effect on physical limitation). The primary objectives are now to determine whether dapagliflozin is superior to placebo in reducing heart failure symptoms, reducing physical limitation, or improving exercise capacity in patients with chronic heart failure. The family of primary endpoints are KCCQ-TSS, KCCQ-PLS, and 6MWD. Most amendments were consequential to the change in primary objectives/endpoints. The secondary objective/endpoint was switched with one of the exploratory objectives/endpoints and exploratory endpoints were revised. The remaining amendments were intended to add clarity and correct minor errors. The following details the key changes: Section 1.2 (Synopsis): Updated to reflect changes in the CSP text, including the changes to the objectives/endpoints as detailed in Section 3. Section 2: (INTRODUCTION) Updated to reflect changes in the objectives/endpoints as detailed in Section 3. Section 3 (OBJECTIVES AND ENDPOINTS): A third primary efficacy objective/endpoint was added (ie, KCCQ-PLS). The secondary objective/endpoint (now 'total time spent in light to vigorous physical activity') was switched with an exploratory objective/endpoint (now 'movement intensity during walking'). The exploratory KCCQ endpoints and the description of the subset of patients to be assessed for certain exploratory measures were revised. Section 4 (STUDY DESIGN): Updated to reflect changes in the objectives/endpoints as detailed in Section 3. Further

	explanation/clarification was added for the choice of primary endpoints. Section 8.1 (Efficacy assessments): Updated to reflect changes in the objectives/endpoints as detailed in Section 3. Section 9 (STATISTICAL CONSIDERATIONS): Updated to reflect changes in the objectives/endpoints as detailed in Section 3, including updated power calculations and methodology for type I error control. General: Minor editing corrections to improve clarity and consistency.

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

Table 1 Schedule of activities

Visit	1 Enrolment	2 Randomisation		3	4 [b] Telephone call	5 Final visit	Early Withdrawal Visit OR Early Treatment Discontinuation Visit [c]	Details in CSP section or Appendix
		2a Randomisation A	2b [a] Randomisation B					
Week	**-2 (±1)**	**0**	**0**	**8 (±1)**	**14 (±1)**	**16 (±1)**		
Day (visit window [±days])	**-14 (±7)**	**1**	**1**	**56 (±7)**	**98 (±7)**	**112 (±7)**		
Informed consent	X							Section 5.1
Inclusion/exclusion criteria	X	X	X					Sections 5.1 and 5.2
Demography	X							Section 5.1
Medical and surgical history	X	X	X					Section 5.1
Concomitant medications	X	X	X	X	X	X	X	Section 6.5
Kansas City Cardiomyopathy Questionnaire [d]	X	X	X	X		X	X	Section 8.1.1.2
Patient global impression of severity in HF symptoms [d]	X	X	X	X		X	X	Section 8.1.1.2
Patient global impression of change in HF symptoms [d]				X		X	X	Section 8.1.1.2
Patient global impression of change in walking ability [d]				X		X	X	Section 8.1.1.2
Dyspnoea, fatigue [d]	X	X	X	X		X	X	Section 8.1.1.2
EQ-5D-5L [d]	X	X	X			X	X	Section 8.1.1.2
Overall treatment benefit [d]				X		X	X	Section 8.1.1.2
Physical examination	X	X	X	X		X	X	Section 8.2.1
NYHA functional classification	X	X	X	X		X	X	Section 8.1.5
12-lead ECG	X							Section 8.2.2

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Day (visit window [±days])	**-14 (±7)**	**1**	**1**	**56 (±7)**	**98 (±7)**	**112 (±7)**		
Vital signs: Systolic and diastolic blood pressure	X	X	X	X		X	X	Section 8.2.3
Vital signs: Pulse rate	X	X	X	X		X	X	Section 8.2.3
Body weight	X	X	X	X		X	X	Section 8.2.4
Height	X							Section 8.2.4
Waist circumference	X	X	X	X		X	X	Section 8.2.4
6-minute walking test [e, f, g]	X [h]	X [i]	X [j]	X		X	X	Section 8.1.1.1
Central laboratory NT-proBNP, sodium, potassium, creatinine/eGFR, haematocrit, HbA1c	X	X	X	X		X	X	Sections 8.1.2 & 8.2.5
Sample for genetic research (if consented)		X	X					Section 8.7; Appendix D
Local pregnancy test using urine β-hCG (female patients of child-bearing potential only)	X	X	X					Section 8.2.5
Randomisation		X	X					
Dispense IP		X	X					
Administer IP dose in clinic for PK assessment		X	X			X	X [k]	

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Week	**-2 (±1)**	**0**	**0**	**8 (±1)**	**14 (±1)**	**16 (±1)**		
Day (visit window [±days])	**-14 (±7)**	**1**	**1**	**56 (±7)**	**98 (±7)**	**112 (±7)**		
PK blood sampling [l]		X	X			X	X [k]	Section 8.5
Wearable activity monitor dispensed, if applicable [m]	X (Monitor B #1 dispensed for immediate use)			X (Monitor B #2 dispensed for immediate use; Monitor B #3 dispensed for delayed use at Week 14)				Section 8.1.3
Collect wearable activity monitor, if applicable [m]		X (Monitor B #1)				X (Monitors B #2 & #3)	X (any monitors)	Section 8.1.3
Telephone call[b] reminding patient to wear activity monitor B #3 and return it at Visit 5 (Final Visit); and to hold IP in the morning of visit 5 (Final visit). IP at visit 5 (Final visit) will be taken at clinic.					X			

Table 1 Schedule of activities

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Week	**-2 (±1)**	**0**	**0**	**8 (±1)**	**14 (±1)**	**16 (±1)**		
Day (visit window [±days])	**-14 (±7)**	**1**	**1**	**56 (±7)**	**98 (±7)**	**112 (±7)**		
Check IP compliance				X		X	X	
Collect unused IP						X	X	
AEs [n]	X	X	X	X	X	X	X	Sections 8.3 & 8.4

[a] Only patients with a difference in 6MWD not within ±15% between Visit 1(Enrolment) and Visit 2a (Randomisation A) need to repeat the assessments at Visit 2b (Randomisation B). The result from the final randomisation visit will be used as the baseline value. See footnote i for calculation example.

[b] Visits 1, 2, 3 and 5 are all clinical visits that are conducted at the study site, while Visit 4 is conducted by telephone with the patient not at the study site. In exceptional cases, for the patient's convenience, it is allowed to conduct this visit on-site.

[c] Patients may withdraw from participating in the study, or they may discontinue taking study medication early but remain in the study (ie, continue attending study visits and completing study assessments). As far as possible, all assessments planned for Visit 5 (Final visit) should be also performed at an Early Withdrawal Visit and at an Early Treatment Discontinuation Visit. At a minimum, safety assessments, PROs, and the 6MWT (if the patient is able) should be performed. Patients who discontinue treatment early but remain in the study may resume taking study medication again as soon as they are able to and wish to. An Unscheduled Visit may be performed at any time after randomisation, if required in the opinion of the Investigator, with the assessments required given in Section 8.

[d] All PROs will be administered using a site-based electronic tablet, except for the patient global impression of change in walking ability and the Borg CR10 Scale® score, which will both be administered on paper. To avoid bias in patient responses, all PRO questionnaires must be completed prior to any other study procedures, following informed consent, except for the Borg CR10 Scale® score, which forms part of the 6MWT. Patients will first complete the patient global impression of change in walking ability followed by the PROs on the site-based electronic tablet, which should all be completed before the 6MWT.

[e] The 6MWT consists of a suite of assessments that are carried out before and after the 6MWT itself: seated pulse rate, blood pressure, oxygen saturation and the Borg CR10 Scale® score for dyspnoea and fatigue.

[f] The 6MWD for each patient, determined from the 6MWT, will first be recorded on paper before being transferred to the eCRF by the Investigator or site staff later.

[g] A number of measures have been introduced to minimise variability in patient performance of the 6MWT. Prior to initiating testing, every effort should be made by the Investigator to establish that the patient is in their "usual" state of health: meaning that the patient has no concurrent medical issues (eg, upper respiratory tract infection, COPD/chronic heart failure exacerbation, exacerbation of musculoskeletal difficulties, etc) that might adversely affect his or her performance of the 6MWT. In the event that such conditions are present, the test should be aborted and rescheduled within a 14 day window, to allow time for the resolution of the acute medical issue and the patient to return to his or her "usual" state of health.

[h] At Visit 1 (Enrolment), if the 6MWD is outside the range of ≥100 metres and ≤425 metres the patient is **NOT** eligible for inclusion **OR** rescreening in the study, and will, thus, be considered a screen failure.

[i] At Visit 2a (Randomisation A), if the 6MWD is outside the range of ≥100 metres and ≤425 metres the patient is **NOT** eligible for inclusion **OR** rescreening in the study, and will, thus, be considered a screen failure. If the 6MWD at Visit 2a (Randomisation A) is within the range of ≥100 metres and ≤425 metres, but the 6MWD recorded at Visit 1 (Enrolment) is not within ±15% of the 6MWD recorded at Visit 2a (Randomisation A), the patient must stop Visit 2a (Randomisation A) immediately; if the difference is within ±15%, the patient can be randomised into the study, with remaining assessments at Visit 2a being completed and does not need to perform Visit 2b (Randomisation B). (Inclusion criterion #7).
Calculation:
Let E be the 6MWD at Visit 1 (Enrolment), let Ra be the 6MWD at Visit 2a (Randomisation A) and let Rb be the 6MWD at Visit 2b (Randomisation B).
The 15% variability criterion at Visit 2a (Randomisation A) is fulfilled if $E \geq Ra*0.85$ and $E \leq Ra*1.15$.
The 15% variability criterion at Visit 2b (Randomisation B) is fulfilled if $Ra \geq Rb*0.85$ and $Ra \leq Rb*1.15$.
Example 1:
If a subject has 6MWD at Visit 1 (Enrolment) equal to 170 metres and 6MWD at Visit 2a (Randomisation A) equal to 200 metres, then the variability is (170-200)/200 which is within ±15% and the subject fulfils the variability requirement in inclusion criterion #7.
Example 2:
If a subject has 6MWD at Visit 1 (Enrolment) equal to 200 metres and 6MWD at Visit 2a (Randomisation A) equal to 170 metres, then the variability is (200-170)/170 which is not within ±15% and the subject does not fulfil the variability requirement in inclusion criterion #7.
Example 3:
If a subject has 6MWD at Visit 2a (Randomisation A) equal to 340 metres and 6MWD at Visit 2b (Randomisation B) equal to 400 metres, then the variability is (340-400)/400 which is within ±15% and the subject fulfils the variability requirement in inclusion criterion #7.

[j] If a patient fails the 6MWD variability, described in inclusion criterion #7, at Visit 2a (Randomisation A) he/she can repeat the 6MWT within 1 week at Visit 2b (Randomisation B). At Visit 2b (Randomisation B), if the 6MWD is outside the range of ≥100 metres and ≤425 metres the patient is **NOT** eligible for inclusion **OR** rescreening in the study, and will, thus, be considered a screen failure. If the 6MWD at Visit 2b (Randomisation B) is within the range ≥100 metres and ≤425 metres, but the 6MWD recorded at Visit 2a (Randomisation A) is not within ±15% of the 6MWD recorded at Visit 2b (Randomisation B) the patient is excluded from the study and considered a screening failure; if the difference is within ±15% the patient can be randomised into the study with the remaining assessments at Visit 2b (Randomisation B) being completed. The result from the final randomisation visit will be used as the baseline value. See the above footnote i for the calculation example.

[k] Applicable only for the early withdrawal visit.

[l] Patients will be reminded not to take IP at home on the days they attend the clinic for Visit 5 (Final visit).

[m] Two distinct types of wearable activity monitor will be used in this study. At a subset of study sites, patients will wear an activity monitor during the 6MWT; this one is for use in the clinic only (wearable activity monitor A), and it is different to the activity monitor that will be dispensed for use at home (wearable activity monitor B). At a subset of study sites, some patients will be dispensed an activity monitor to wear at home.

[n] SAEs will be collected from the time of providing informed consent, and non-serious AEs will be collected from the time of randomisation.

6MWD 6-minute walk distance; 6MWT 6-minute walk test; AEs adverse events; β-hCG beta human chorionic gonadotropin; COPD chronic obstructive pulmonary disease; CSP Clinical Study Protocol; ECG electrocardiogram; eCRF electronic case report form; eGFR estimated glomerular filtration rate; EQ-5D-5L European Quality of Life 5-dimension 5-level questionnaire; HbA1c glycated haemoglobin; HF heart failure; IP investigational product; NT-proBNP N-terminal pro b-type natriuretic peptide; NYHA New York Heart Association; PK pharmacokinetic; PRO patient-reported outcome

1.2 Synopsis

International co-ordinating investigator

USA

Protocol Title:

An International, Multicentre, Parallel-group, Randomised, Double-blind, Placebo-controlled, Phase III Study Evaluating the effect of Dapagliflozin on Exercise Capacity in Heart Failure Patients with Preserved Ejection Fraction (HFpEF)

Short Title:

DETERMINE-preserved - Dapagliflozin EffecT on ExeRcise capacity using a 6-MINutE walk test in patients with heart failure with preserved ejection fraction

Rationale:

The prevalence of chronic heart failure continues to increase globally, and the annual global economic burden (several hundred billion dollars in 2012) will increase as the population ages. Recent data from cardiovascular outcome studies of sodium-glucose co-transporter-2 inhibitors (empagliflozin and canagliflozin) and real world studies (including patients treated with dapagliflozin) indicate that treatment with sodium-glucose co-transporter-2 inhibitors can reduce the risk of cardiovascular death and hospitalisation due to heart failure in patients with Type 2 diabetes mellitus (T2DM) overall and in patients with T2DM and concomitant heart failure. Additional important endpoints in heart failure patients include assessment of change in heart failure symptoms, physical limitation, and exercise capacity. This study will test whether dapagliflozin is superior to placebo for change in any of the family of 3 primary endpoints: Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS); Kansas City Cardiomyopathy Questionnaire Physical Limitation Score (KCCQ-PLS); or, 6-minute walk distance (6MWD) from baseline at Week 16, in patients with chronic heart failure (New York Heart Association [NYHA] Functional Class II-IV) and preserved left ventricular ejection fraction (>40%), with or without T2DM.

Objectives and Endpoints

Primary Objectives:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and preserved ejection fraction (LVEF>40%) [HFpEF] in: • reducing patient-reported HF symptoms • reducing patient-reported physical limitation • improving exercise capacity	Family of primary endpoints: • Change from baseline in the KCCQ-TSS at Week 16. • Change from baseline in the KCCQ-PLS at Week 16. • Change from baseline in 6MWD at Week 16.
Secondary Objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in increasing time spent non-sedentary, evaluated in a subset of at least 100 patients	Change from baseline at the end of the study in total time spent in light to vigorous physical activity, as assessed using a wearable activity monitor (accelerometer).
Safety objective:	**Variables:**
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF	• AEs • SAEs • DAEs • AEs leading to amputation • Potential risk factor AEs for amputations affecting lower limbs • Laboratory tests • Vital signs
Exploratory Objectives:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in increasing total physical activity, evaluated in a subset of at least 100 patients	Change from baseline at end of study in total activity measured by vector magnitude units per minute, as assessed using a wearable activity monitor (accelerometer).
To determine whether dapagliflozin is superior to placebo in reducing serum NT-proBNP	Change from baseline in serum NT-proBNP at Week 16.
To determine whether dapagliflozin is superior to placebo in increasing the exercise capacity during daily life, evaluated in a subset of at least 100 patients	Change from baseline at end of study in movement intensity during walking, as assessed using a wearable activity monitor (accelerometer).
To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA Functional Classification	Proportion of patients with worsened NYHA Functional Classification at Week 16.
To compare the effect of dapagliflozin versus placebo on physical activity, evaluated in a subset of at least 100 patients	Change from baseline at end of study for exploratory endpoints assessed using wearable activity monitors (accelerometers), in amount, duration and intensity.
To compare the effect of dapagliflozin versus placebo on health status as assessed by EQ-5D-5L	Change from baseline in health status utilities as measured by EQ-5D-5L at Week 16.
To compare the effect of dapagliflozin versus placebo on patient reported dyspnoea and fatigue	Change from baseline in dyspnoea at Week 16. Change from baseline in fatigue at Week 16.

Objectives and Endpoints

To assess the patients' overall evaluation of net treatment benefit	Distribution of patients' assessment of benefit of IP.
To explore whether dapagliflozin compared to placebo improves symptom frequency, symptom burden, symptom stability, social limitation, and QoL	Changes from baseline in the following KCCQ domains at Week 16: • TSS domains: symptom burden and symptom frequency • Overall summary score • Symptom stability domain • Self-efficacy domain • Social limitation domain • QoL domain
To assess change in oxygen saturation after 6MWT	Change from baseline in oxygen saturation difference after 6MWT at Week 16.
To determine whether dapagliflozin compared with placebo has an effect on systolic BP	Change from baseline in systolic BP at Week 16.
To determine whether dapagliflozin compared with placebo has an effect on body weight	Change from baseline in body weight at Week 16.
To determine whether dapagliflozin compared with placebo has an effect on eGFR.	Change from baseline in eGFR at Week 16.
To collect and store blood samples for PK assessment	Explore dapagliflozin exposure-response relationship for efficacy and safety endpoints. The results will be analysed and reported in a separate report.
To collect and store blood samples for future exploratory genetic samples	Not applicable. Results will be analysed and reported separately.

6MWD 6-minute walk distance; 6MWT 6-minute walk test; AE adverse event; BP blood pressure; DAE adverse event leading to discontinuation of investigational product; eGFR estimated glomerular filtration rate; EQ-5D-5L European Quality of Life 5-dimensional 5-level health status questionnaire; HF heart failure; HFpEF heart failure with preserved ejection fraction; IP investigational product; KCCQ Kansas City Cardiomyopathy Questionnaire; LVEF left-ventricular ejection fraction; NT-proBNP N-terminal pro b-type natriuretic peptide; NYHA New York Heart Association; PK pharmacokinetic; PLS Physical Limitation Score; QoL Quality of Life; SAE serious adverse event; TSS total symptom score

Overall design

This is an international, multi-centre, parallel-group, randomised, double-blind, placebo-controlled, phase III study in heart failure patients with preserved left ventricular ejection fraction, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background local standard of care therapy, including treatments to control co-morbidities, on change in heart failure symptoms as measured by the KCCQ-TSS, physical limitation as measured by the KCCQ-PLS, and exercise capacity as measured by 6MWD. Adult patients aged ≥40 years with chronic heart failure with preserved left ventricular ejection fraction (>40% and evidence of structural heart disease) and NYHA Functional

Class II-IV, who meet all of the inclusion criteria and none of the exclusion criteria, will be randomised 1:1 to receive either dapagliflozin 10 mg or matching placebo. Randomisation will be stratified by the presence or absence of T2DM. It is estimated that approximately 1000 patients will need to be enrolled to reach the target of approximately 500 randomised patients.

Study period

Estimated date of first patient enrolled Q1 2019.

Estimated date of last patient completed Q3 2020.

Number of patients

Approximately 1000 patients will be enrolled to reach a target of approximately 500 randomised patients, assuming a screening failure rate of 50%.

Treatments and treatment duration

Patients who meet all of the inclusion criteria and none of the exclusion criteria, will be randomised 1:1 to receive either once daily dapagliflozin 10 mg or matching placebo. Treatment should start within 24 hours after randomisation and the anticipated average treatment duration is 16 weeks.

Data Monitoring Committee

Due to the short duration of the study and the accumulated safety profile of dapagliflozin, a separate independent data monitoring committee will not be necessary to assess patient safety during this study. However, 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, with all reviewers blinded to the study treatments.

Statistical methods

The primary objectives of the study are to determine whether dapagliflozin is superior to placebo in reducing heart failure symptoms, reducing physical limitation, or improving exercise capacity in patients with chronic heart failure. The study will randomise approximately 500 patients (approximately 250 patients per treatment group). This sample size estimate is based on the primary efficacy endpoints (change from baseline in KCCQ-TSS, KCCQ-PLS, and 6MWD at Week 16). Randomisation will be stratified by presence or absence of T2DM.

Efficacy analysis

The primary and secondary efficacy endpoints will be evaluated under a combined treatment policy (intent-to-treat) and composite variable strategy estimand, including differences in the

outcome variable at the end of the 16-week treatment period. The intent-to-treat approach is employed to reflect the effect of the initially assigned randomised study drug, irrespective of exposure to study drug and concomitant treatment as well as subsequent treatment after discontinuation of study drug. A composite variable strategy approach is employed to account for deaths occurring during the follow-up period.

The family of primary efficacy endpoints (KCCQ-TSS, KCCQ-PLS, and 6MWD) will be analysed based on a rank analysis of covariance model with rank-based change from baseline at Week 16 as the dependent variable. Rank-based baseline value will be included as a covariate along with the stratification factor used in the randomisation. Ties will be assigned the mean of the corresponding ranks. In this analysis, data that are missing due to death will be ranked "worse" than observed data and data missing for reasons other than death, and the ranking amongst the deceased patients will be based on the last value while alive. Missing data due to reasons other than death (eg, missing visits, early withdrawal from the study, including lost to follow-up) will be replaced by multiple imputation with predictive mean matching. Rank analysis of covariance will then be applied to each imputation dataset and results will be pooled across datasets.

The magnitude of treatment effect in each of the KCCQ-TSS and KCCQ-PLS will also be presented as the number and percentage of patients by treatment group across the following categories of change from baseline:

- Death
- Deterioration from baseline (change from baseline $\leq$-5)
- Stable (-5< change from baseline <5)
- Improvement (change from baseline $\geq$5)

The magnitude of treatment effect in 6-minute walk distance will also be presented as the number and percentage of patients by treatment group across the following categories of change from baseline:

- Death
- No improvement from baseline (change from baseline $\leq$0 metres)
- Minimal improvement (0< change from baseline <30 metres)
- Improvement (change from baseline $\geq$30 metres)

Clinical meaningfulness has not been demonstrated for the pre-specified categories. Therefore, thresholds for clinically meaningful within-patient change for KCCQ-TSS, KCCQ-PLS, and 6MWD will be assessed using pre-specified methods described in the Statistical Analysis Plan and the derived thresholds will be the main categories used to assess the magnitude of treatment effect.

To provide a visual display of the relative benefit of dapagliflozin over placebo across different ranges of response at Week 16, empirical cumulative distribution functions for each treatment group will be presented.

The type I error rate will be controlled to support superiority claims for dapagliflozin compared with placebo. The overall type I error (alpha) will initially be split between the KCCQ-TSS, KCCQ-PLS, and 6MWD. Testing will proceed to the secondary endpoint if statistical significance is demonstrated for at least 1 endpoint in the primary endpoint family. The testing procedure will be described in detail in the Statistical Analysis Plan.

Safety analysis

Safety analyses will be performed using the Safety Analysis Set, consisting of all patients who received one dose of investigational product. Safety data will be summarised descriptively by actual treatment received and will not be formally tested.

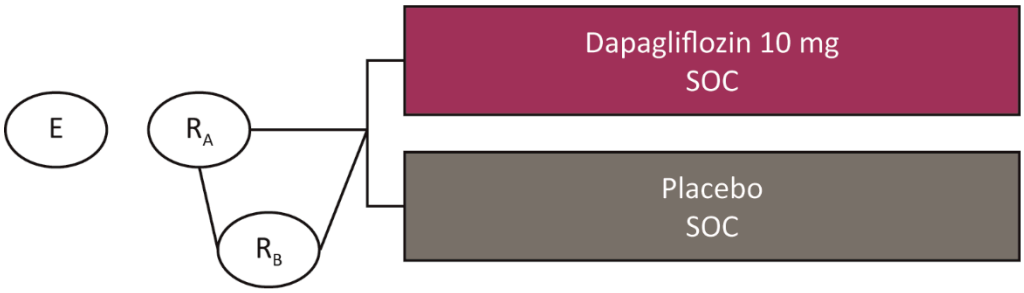
Sample size estimate

Enrolment in this study is intended to yield approximately 500 patients randomised to treatment. This sample size estimate is based on the primary endpoints of KCCQ-TSS, KCCQ-PLS, and 6MWD, as well as the assumption that mortality over the entire 16-week treatment period is about 5% in each treatment arm.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Visit	**E**	**R_A**	**R_B** [a]		**T**	**FV**
	1	2a	2b [a]	3	4	5
Week	-2 ±1	0	0 [a]	8 ±1	14 ±1	16 ±1
Day	-14 ±7	1	1 [a]	56 ±7	98 ±7	112 ±7

[a] Visit 2b occurs within 7 days of Visit 2a and constitutes Week 0 and Day 1 for patients who qualify for Randomisation B.

E Enrolment; FV Final visit; R_A Randomisation A; R_B Randomisation B; SOC Standard of care; T telephone call

2 INTRODUCTION

2.1 Study rationale

Chronic heart failure (HF) continues to be a major cause of mortality, hospitalisations and suboptimal quality of life. Even with the best possible treatment, the five-year survival rate for HF patients is worse than for most cancers (Braunwald 2015). Moreover, 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.

HF 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); this study investigates patients with the latter.

For the purposes of this study, HFpEF is defined as LVEF >40% (HFrEF is usually defined as LVEF ≤40%). It should be noted that HF patients with a LVEF value of 40% to 50% often represent a separate population (Ponikowski et al 2016). Therefore, in this study, patients with a LVEF value above 40% and below 50% will be evaluated as a subgroup in supportive analyses. The proportion of patients in the study with a LVEF value above 40% and below 50% at baseline will be monitored to ensure that the majority of patients have an LVEF value above 50%.

Approximately half of all HF 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). 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 can improve symptoms and haemodynamics as well as reduce hospitalisations for HF 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 outcome studies of sodium-glucose co-transporter-2 (SGLT2) inhibitors (empagliflozin and canagliflozin) indicate that treatment with SGLT2 inhibitors can reduce the risk of cardiovascular death and hospitalisation due to HF in patients with Type 2 diabetes mellitus (T2DM) overall, and in patients with T2DM and concomitant

HF (Zinman et al 2015; Ferreira et al 2016; Fitchett et al 2016; Neal et al 2017; Rådholm et al 2018).

In this study, patients will be treated with the SGLT2 inhibitor, dapagliflozin, or matching placebo and their changes in HF symptoms, physical limitation, and exercise capacity over 16 weeks will be assessed. Patients' HF symptoms and physical limitation will be measured using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) and Kansas City Cardiomyopathy Questionnaire Physical Limitation Score (KCCQ-PLS), respectively. Patients' exercise capacity will be measured using the 6-minute walk test (6MWT; the distance a patient can walk in a 6-minute period, the 6MWD). The 6MWT is a standard method (Holland et al 2014, American Thoracic Society 2002) for measuring the exercise response to medical interventions in patients with moderate to severe heart or lung disease, having already been used to give pre-treatment and post-treatment comparisons for patients with HF (DeBock et al 1994, O'Keeffe et al 1998). In addition, patient health-related quality of life will be assessed using various patient-reported outcome (PRO) measures. The intention is to determine whether, with once daily administration over a 16-week period, 10 mg dapagliflozin is superior to placebo for reducing HF symptoms, reducing physical limitation, or improving exercise capacity in patients with HFpEF.

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. Observations from the overall dapagliflozin clinical development programme suggest that dapagliflozin may increase exercise capacity in HFpEF patients (as a surrogate measure of daily activity) irrespective of diabetes status. Dapagliflozin lowers glycated haemoglobin (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 cardiovascular and renal risk (Shigiyama et al 2017). Dapagliflozin is believed to be nephroprotective through non-glycaemic mechanisms (Wanner et al 2016).

In combination, the identified blood pressure- and body weight-lowering effects of dapagliflozin, may help to increase the exercise capacity in the HFpEF population, a population with a high prevalence of hypertension and obesity. The findings from EMPA-REG OUTCOME study (Fitchett et al 2016), with a similar SGLT2 inhibitor compound, suggests that kidney function is preserved, or improved, in this diabetic study population. Furthermore, HFpEF patients are characterised by fluid retention and a change in cardiac metabolism favouring glucose as substrate, both of which have been hypothesised to be affected positively 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 (Borlaug and Paulus 2011).

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

This is an international, multi-centre, parallel-group, randomised, double-blind, placebo-controlled, phase III study in HFpEF patients, evaluating the effect of dapagliflozin 10 mg versus placebo (given once daily in addition to background local standard of care therapy, including treatments to control co-morbidities) on change in HF symptoms as measured by KCCQ-TSS, physical limitation as measured by KCCQ-PLS, and exercise capacity as measured by 6MWD.

2.3 Benefit/risk assessment

Dapagliflozin has global marketing approval in more than 90 countries. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of dapagliflozin may be found 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

The safety profile of dapagliflozin is already well established from clinical studies for T2DM and type 1 diabetes mellitus and is generally safe and well-tolerated.

Dapagliflozin, as an inhibitor of SGLT2, increases urinary glucose excretions, which is commonly believed to increase the risk of urinary tract infections. Urinary tract infections have been reported in dapagliflozin-treated patients in a slightly higher proportion than in placebo-treated patients in some global phase III studies. Increased urinary glucose excretion may also lead to an increased risk of developing genital infections. Urinary tract infections are considered a common side effect (in ≥1/100 to <1/10 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 T2DM programme, 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 T2DM and HF in the dapagliflozin development programme, showed no increase of volume depletion events, but an increase in renal events, mainly creatinine increases, in patients treated with dapagliflozin (n=171)

compared with patients treated with placebo (n=149). About half of the patients were on loop diuretics (Kosiborod et al 2017).

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 programme that dapagliflozin is associated with an increased risk of amputation (further information provided in Section 8.3.1.1 for the detection and capture of events leading to amputation).

Dapagliflozin has not been shown to induce hypoglycaemia in non-diabetic patients. In clinical pharmacology studies, healthy subjects have been treated with single oral doses of 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 T2DM taking dapagliflozin and other SGLT2 inhibitors. Diabetic ketoacidosis is considered a rare (in ≥1/10000 to <1/1000 patients) adverse drug reaction for dapagliflozin in patients with T2DM.

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 evaluated promptly.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (eg, type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements caused by 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 type-1 diabetes mellitus; 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 AEs potentially placing the patient at risk of a lower limb amputation will be collected (Section 8.3.1.1). 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. Because of the short duration of the study and the accumulated safety profile of dapagliflozin, an independent Data Monitoring Committee will not be used in this study.

2.3.2 Potential benefits to patients

All patients in the study are expected to be treated optimally according to background local standard of care therapy, including treatments to control co-morbidities. Dapagliflozin or matching placebo will be administered on top of these treatments.

All patients participating in clinical studies, 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 nonclinical 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 T2DM with HF, no available SGLT2 inhibitor has a treatment indication for patients with HFpEF. This clinical study will test the hypothesis that dapagliflozin is superior to placebo in reducing patient-reported HF symptoms, reducing physical limitation, or improving exercise capacity in patients with HFpEF, with or without T2DM, in a rigorous fashion. The results could offer substantial benefit to patients with HFpEF, a patient population with a large medical need for effective treatments.

3 OBJECTIVES AND ENDPOINTS

Table 2 Study objectives

Primary Objectives:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and preserved ejection fraction (LVEF>40%) [HFpEF] in: • reducing patient-reported HF symptoms • reducing patient-reported physical limitation • improving exercise capacity	Family of primary endpoints: • Change from baseline in the KCCQ-TSS at Week 16. • Change from baseline in the KCCQ-PLS at Week 16. • Change from baseline in 6MWD at Week 16.
Secondary Objective:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in increasing time spent non-sedentary, evaluated in a subset of at least 100 patients	Change from baseline at the end of the study in total time spent in light to vigorous physical activity, as assessed using a wearable activity monitor (accelerometer).

Table 2 Study objectives

Safety objective:	**Variables:**
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF	• AEs • SAEs • DAEs • AEs leading to amputation • Potential risk factor AEs for amputations affecting lower limbs • Laboratory tests • Vital signs
Exploratory Objectives:	**Endpoint/variable:**
To determine whether dapagliflozin is superior to placebo in increasing total physical activity, evaluated in a subset of at least 100 patients	Change from baseline at end of study in total activity measured by vector magnitude units per minute, as assessed using a wearable activity monitor (accelerometer).
To determine whether dapagliflozin is superior to placebo in reducing serum NT-proBNP	Change from baseline in serum NT-proBNP at Week 16.
To determine whether dapagliflozin is superior to placebo in increasing the exercise capacity during daily life, evaluated in a subset of at least 100 patients	Change from baseline at end of study in movement intensity during walking, as assessed using a wearable activity monitor (accelerometer).
To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA Functional Classification	Proportion of patients with worsened NYHA Functional Classification at Week 16.
To compare the effect of dapagliflozin versus placebo on physical activity, evaluated in a subset of at least 100 patients	Change from baseline at end of study for exploratory endpoints assessed using wearable activity monitors (accelerometers), in amount, duration and intensity.
To compare the effect of dapagliflozin versus placebo on health status as assessed by EQ-5D-5L	Change from baseline in health status utilities as measured by EQ-5D-5L at Week 16.
To compare the effect of dapagliflozin versus placebo on patient reported dyspnoea and fatigue	Change from baseline in dyspnoea at Week 16. Change from baseline in fatigue at Week 16.
To assess the patients' overall evaluation of net treatment benefit	Distribution of patients' assessment of benefit of IP.
To explore whether dapagliflozin compared to placebo improves symptom frequency, symptom burden, symptom stability, social limitation, and QoL	Changes from baseline in the following KCCQ domains at Week 16: • TSS domains: symptom burden and symptom frequency • Overall summary score • Symptom stability domain • Self-efficacy domain • Social limitation domain • QoL domain
To assess change in oxygen saturation after 6MWT	Change from baseline in oxygen saturation difference after 6MWT at Week 16.

Table 2 Study objectives

To determine whether dapagliflozin compared with placebo has an effect on systolic BP	Change from baseline in systolic BP at Week 16.
To determine whether dapagliflozin compared with placebo has an effect on body weight	Change from baseline in body weight at Week 16.
To determine whether dapagliflozin compared with placebo has an effect on eGFR.	Change from baseline in eGFR at Week 16.
To collect and store blood samples for PK assessment	Explore dapagliflozin exposure-response relationship for efficacy and safety endpoints. The results will be analysed and reported in a separate report.
To collect and store blood samples for future exploratory genetic samples	Not applicable. Results will be analysed and reported separately.

6MWD 6-minute walk distance; 6MWT 6-minute walk test; AE adverse event; BP blood pressure; DAE adverse event leading to discontinuation of investigational product; eGFR estimated glomerular filtration rate; EQ-5D-5L European Quality of Life 5-dimensional 5-level health status questionnaire; HF heart failure; HFpEF heart failure with preserved ejection fraction; IP investigational product; KCCQ Kansas City Cardiomyopathy Questionnaire; LVEF left ventricular ejection fraction; NT-proBNP N-terminal pro b-type natriuretic peptide; NYHA New York Heart Association; PK pharmacokinetic; PLS Physical Limitation Score; QoL Quality of Life; SAE serious adverse event; TSS total symptom score

4 STUDY DESIGN

4.1 Overall design

This is an international, multi-centre, parallel-group, randomised, double-blind, placebo-controlled, phase III study in HFpEF patients, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to background local standard of care therapy, including treatments to control co-morbidities, on change in HF symptoms as measured by KCCQ-TSS, physical limitation as measured by KCCQ-PLS, and exercise capacity as measured by 6MWD.

An overview of the study design is provided in Figure 1, Section 1.3. Details on treatments given during the study are provided in Section 6.1.

Details on what is included in the efficacy and safety endpoints are provided in Section 3.

Adult patients with chronic HFpEF (defined for the purposes of this study as LVEF >40% and evidence of structural heart disease, ie, left atrial enlargement and or left ventricular hypertrophy) and New York Heart Association (NYHA) Functional Class II-IV, aged ≥40 years who meet the all of the inclusion criteria and none of the exclusion criteria, will be randomised 1:1 to receive either dapagliflozin 10 mg or matching placebo. Randomised treatment should be started as soon as possible. It is estimated that approximately 1000 patients will need to be enrolled to reach the target of approximately 500 randomised

patients, assuming a screening failure rate of 50%. The rationale for the sample size determination is given in Section 9.2.

In this study the recruitment of patients between sites will be competitive. Data on baseline characteristics, endpoints and AEs will be collected through a validated web-based data capture system.

4.2 Scientific rationale for study design

This is a randomised, multi-centre, double-blind, placebo-controlled, parallel-group, phase III study. Randomisation and double-blinding will minimise potential bias.

The study population will include patients both with and without T2DM, 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 will be capped on a study level based on the proportion of patients with and without T2DM and the proportion of patients with an LVEF value above 40% and below 50%, and atrial fibrillation/flutter status will be monitored to ensure they are representative.

The control group will receive matching placebo; there are no approved pharmacological treatments for HFpEF that could be used 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 (eg, diuretics) and co-morbidities (including treatment for high blood pressure, ischaemic heart disease, and atrial fibrillation/flutter). Each patient is to be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual (with respect to HF symptoms, renal function, blood pressure, and electrolyte status).

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

The primary efficacy endpoints of the study are change from baseline in each of KCCQ-TSS, KCCQ-PLS, and 6MWD at Week 16. The KCCQ is a disease-specific PRO measure developed for patients with chronic HF. The KCCQ has shown to be a valid, reliable and responsive measure of HF symptoms (as measured by KCCQ-TSS) and physical limitation (as measured by KCCQ-PLS) (Greene et al 2018, Spertus et al 2005). Such measures have been shown to be clinically meaningful endpoints in patients with HF (Ferreira et al 2016).

Although the 5-point threshold for clinically meaningful within-patient change has not been demonstrated specifically for the KCCQ-TSS or KCCQ-PLS in published clinical trials, the

use of this pre-specified threshold in the DETERMINE studies is supported by its extensive use in other KCCQ scales, including the KCCQ-OSS of which the KCCQ-TSS is a part (Filippatos et al 2017, Comin-Colet et al 2013). Furthermore, its use for KCCQ-TSS and KCCQ-PLS is supported by other studies (Spertus et al 2005, Dreyer et al 2016). Appropriate thresholds for clinically meaningful within-patient change will be evaluated using anchor-based methods, which are described in the Statistical Analysis Plan (SAP).

The rationale for assessing change in 6MWD is that the 6MWT (the test used to determine the 6MWD) can act as a surrogate of normal daily activity. The 6MWT is a standard method for measuring exercise response (Holland et al 2014, American Thoracic Society 2002) to medical interventions in patients with moderate to severe heart or lung disease, giving clinically meaningful change (Shoemaker et al 2012), having already been used to give pre-treatment and post-treatment comparisons for patients with HF (DeBock et al 1994, O'Keeffe et al 1998).

Reviews of the literature for clinically relevant thresholds for 6MWT in HF support a 30 m threshold for clinically important difference (Shoemaker et al 2013). An older study of 45 patients (O'Keeffe et al 1998) reported that patients who reported feeling "a bit better" had a mean within-patient change in 6MWD of 24 m, and patients who reported "much better" had a mean within-patient change of 47 m. Data from chronic respiratory disease studies provides the most comprehensive evidence base for clinically relevant 6MWT change thresholds. The most recent European Respiratory Society/American Thoracic Society Technical Standard (Holland et al 2014) states that the minimal important difference lies between 25 and 33 metres. This is also consistent with a recent review (Ferreira et al 2016) by leading experts in HF. However, these are based on group-level estimates and not within-patient change. Appropriate thresholds for clinically meaningful within-patient change in the target population will be evaluated using anchor-based methods, with patient global impression of severity (PGIS) and patient global impression of change (PGIC) instruments, which are described in the SAP.

Finally, patients will also complete a suite of PRO measures (eg, rating of dyspnoea and fatigue, and overall treatment benefit [OTB]), to help support the primary endpoints.

4.3 Justification for dose

The 10 mg dose of dapagliflozin has a well-characterised efficacy and safety profile in the T2DM clinical development programme and is the recommended dose in the majority of countries worldwide.

From a pharmacokinetic (PK) 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 because there is no evidence 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 the dapagliflozin clinical programme, there are no dose-related serious adverse events (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 T2DM in placebo-controlled clinical studies, dapagliflozin 10 mg was found to be well-tolerated (Kosiborod et al 2017).

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 10 mg dapagliflozin resulted in improvements in parameters associated with arterial remodelling in addition to lowering blood pressure in patients with T2DM (Ott et al 2017). This 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 visit/contact of the last patient participating in the study.

A patient is considered to have completed the study when he/she has completed Visit 5 (Final visit) even if the patient discontinues treatment during the study, but remains in the study until Visit 5 (Final visit). By contrast, patients who prematurely withdraw, or who are prematurely withdrawn, from the study, are considered as non-completers.

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. 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.

Guidelines for the dissemination of study results are given in Appendix A 6.

5 STUDY POPULATION

In this study, patients will usually be recruited from sites involved in routine cardiology clinical practice.

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomised to investigational product (IP). Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures (Section 5.4).

In this protocol, "enrolled" patients are defined as those who sign the informed consent form (ICF). "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number.

Procedures for withdrawal of incorrectly enrolled patients are given in Section 7.3.

5.1 Inclusion criteria

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

1 Provision of signed informed consent (including genetic sampling if applicable) prior to any study specific procedures are performed. The ICF process is described in Appendix A 3.

2 Male or female patients aged ≥40 years on the day consent given.

3 Documented diagnosis of symptomatic HF (NYHA Functional Class II-IV) at enrolment, and a medical history of typical symptoms/signs of HF[1] >8 weeks before enrolment, which is optimally treated with pharmacotherapy and/or device therapy (detailed in note below), as indicated, with at least intermittent need for diuretic treatment.

Note: Patients for whom additional pharmacological or device therapy is contemplated, or should be considered, must not be enrolled until therapy has been optimised and is stable for ≥4 weeks.

4 LVEF >40% and evidence of structural heart disease (ie, left ventricular hypertrophy or left atrial enlargement[2]) documented by the most recent echocardiogram, or cardiac magnetic resonance imaging within the last 12 months prior to enrolment (Visit 1).

Note: for all patients:

If there is more than 1 assessment of LVEF, the value from the most recent measurement should be used in assessing eligibility. The LVEF should be reported by the Investigator as a single value; if only a range of LVEF is available which includes 40%, a repeat echocardiogram should be performed as part of screening.

Patients with known HF but without a recent (≤12 months) assessment of left ventricular function will undergo a local echocardiogram at the time of enrolment (Visit 1).

For patients with prior acute cardiac events (eg, as defined in Exclusion Criterion 9), or procedures (eg, percutaneous coronary intervention, coronary artery bypass grafting, valve repair or replacement, implantation of cardiac resynchronisation therapy device or any other surgical, device or pharmacological intervention [eg, initiation of beta-blocker]) that might change LVEF, or pharmaceutical therapies that may change LVEF, qualifying cardiac imaging assessment must be obtained at least 12 weeks following the procedure/event/therapy.

5 NT-proBNP ≥250 pg/mL (≥29.51 pmol/L) at Visit 1 for patients without ongoing atrial fibrillation/flutter. If atrial fibrillation/flutter is present at Visit 1, NT-proBNP must be ≥500 pg/mL (≥59.08 pmol/L).

Note: For the purpose of this study, atrial fibrillation/flutter must be present on ECG performed on Visit 1 to be considered present.

6 Patients should receive background standard of care as described below:

All patients will be treated according to locally recognised guidelines on standard of care treatment for patients with HFpEF. Therapy should have been individually optimised and stable for ≥4 weeks (this does not apply to diuretics – see Note, below) and include (unless

contraindicated or not tolerated) treatment of co-morbidities (including high blood pressure, ischaemic heart disease, atrial fibrillation/flutter).

Note: Most patients with HF require treatment with a diuretic to control sodium and water retention leading to volume overload. It is recognised that diuretic dosing may be titrated to symptoms, signs, weight and other information and may thus vary. Each patient should, however, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual (with respect to HF symptoms, renal function, blood pressure, and electrolyte status). Specifically, patient volume status should be individually optimised on a stable dose of diuretics for at least 2 weeks prior to screening.

Note: Optimised and stable treatment applies also past Visit 1 and until patient is randomised.

7 6MWD ≥100 metres and ≤425 metres at both the Enrolment and Randomisation A and Randomisation B (Visits 1 and 2a and 2b).

Note: To further minimise testing variability due to patient performance, baseline 6MWD will be compared at the Enrolment (Visit 1) and Randomisation A (Visit 2a). If the 6MWD (at Visit 1 [Enrolment]) is within ±15% of the 6MWD observed at Randomisation A, the patient is randomised. If this 15% requirement is not met, the patient will undergo a third test at Randomisation B (Visit 2b), within 1 week after Randomisation A. The 6MWD obtained at Randomisation A should be within ±15% of the value obtained at Randomisation B. If this requirement is met, the patient is randomised at Randomisation B. If the 15% requirement is not met, the patient cannot be included in the study. The patient is not eligible for rescreening due to a failure to meet the variability criteria for 6MWD.

Let E be the 6MWD at Visit 1 (Enrolment), let Ra be the 6MWD at Visit 2a (Randomisation A) and let Rb be the 6MWD at Visit 2b (Randomisation B). The 15% variability criterion at Visit 2a (Randomisation A) is fulfilled if $E \geq Ra*0.85$ and $E \leq Ra*1.15$. The 15% variability criterion at Visit 2b (Randomisation B) is fulfilled if $Ra \geq Rb*0.85$ and $Ra \leq Rb*1.15$.

Example 1:
If a subject has 6MWD at Visit 1 (Enrolment) equal to 170 metres and 6MWD at Visit 2a (Randomisation A) equal to 200 metres, then the variability is (170-200)/200 which is within ±15% and the subject fulfils the variability requirement in inclusion criterion #7.
Example 2:
If a subject has 6MWD at Visit 1 (Enrolment) equal to 200 metres and 6MWD at Visit 2a (Randomisation A) equal to 170 metres, then the variability is (200-170)/170 which is not within ±15% and the subject does not fulfil the variability requirement in inclusion criterion #7.
Example 3:
If a subject has 6MWD at Visit 2a (Randomisation A) equal to 340 metres and 6MWD at Visit

2b (Randomisation B) equal to 400 metres, then the variability is (340-400)/400 which is within ±15% and the subject fulfils the variability requirement in inclusion criterion #7.

If the 6MWD is outside of ≥100 metres and ≤425 metres at any visit until randomisation is completed, the patient is no longer eligible to continue in the study, is not eligible for rescreening, and should be withdrawn from the study.

5.2 Exclusion criteria

1 Presence of any condition that precludes exercise testing such as:
   (a) claudication that limits exertion
   (b) uncontrolled bradyarrhythmia or tachyarrhythmia (according to Investigator judgement)
   (c) clinically significant musculoskeletal disease or orthopaedic conditions that limit the ability to walk (eg, arthritis or injury in the foot, leg, knee or hip)
   (d) pulmonary diagnoses (as described in note below)
   (e) severe obesity (body mass index ≥50.0 kg/m^2)
   (f) amputation with artificial limb without stable prosthesis function for the past 3 months
   (g) any condition that, in the opinion of the Investigator, would contraindicate the assessment of 6MWT (eg, severe visual impairment)
   (h) any condition other than HF that, in the opinion of the Investigator, is the primary limitation to exercise

Note: Although patients with stable pulmonary and musculoskeletal disease may be included in this study, these conditions must not be the primary cause for activity limitation. These patients must be optimally treated and their pulmonary or musculoskeletal condition considered stable to be able to participate in the study.

2 Participation in a structured exercise training programme in the 1 month prior to screening or planned to start during the trial.

Note: 1 month is interpreted as 4 weeks.

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

4 Type 1 diabetes mellitus.

5 eGFR <25 mL/min/1.73 m^2 (chronic kidney disease-epidemiology collaboration [CKD-EPI] formula) at Visit 1 (Enrolment), unstable or rapidly progressing renal disease at the time of randomisation.

6 Systolic blood pressure (BP) <95 mmHg on 2 consecutive measurements at 5-minute intervals, at Visit 1, or at Visit 2a or Visit 2b (Randomisation A or Randomisation B).

7 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 (Enrolment) or at Visit 2a or Visit 2b (Randomisation A or Randomisation B).

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

9 Myocardial infarction, unstable angina, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial fibrillation/flutter, valve repair/replacement, implantation of a cardiac resynchronisation therapy device within 12 weeks prior to enrolment. Before enrolment, these patients must have their qualifying LVEF assessment at least 12 weeks after the event.

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

11 Stroke or transient ischemic attack within 12 weeks prior to enrolment.

12 Probable alternative or concomitant diagnoses which in the opinion of the Investigator could account for the patient's HF symptoms and signs (eg, anaemia, hypothyroidism).

13 Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (ie, 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).

14 Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronisation therapy. Prior implantation of a ventricular assistance device or similar device, or implantation expected after randomisation.

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

16 A life expectancy of <2 years due to any non-cardiovascular condition, based on Investigator's clinical judgement.

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

18 Acute or chronic liver disease with severe impairment of liver function (eg, ascites, oesophageal varices, coagulopathy).

19 Women of child-bearing potential (ie, those who are not chemically or surgically sterilised or post-menopausal):

   (a) Who are not willing to use a medically accepted method of contraception considered reliable in the judgment of the Investigator, OR

(b) Who have a positive urine pregnancy test at Visit 1 (Enrolment) or at Visit 2a or Visit 2b (Randomisation A or Randomisation B), OR

(c) Who are breast-feeding.

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

21 Previous randomisation in the present study.

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

23 Inability of the patient, in the opinion of the Investigator, to understand and/or comply with study medications, procedures and/or follow-up (especially completing ePRO assessments) OR any conditions that, in the opinion of the Investigator, may render the patient unable to complete the study. Therefore, patients who are unable to read (eg, are blind or illiterate) should be excluded from participating in this trial.

5.3 Lifestyle restrictions (not applicable)

5.4 Screen failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomised to a study treatment. Any patient who does not fulfil **all** inclusion criteria or who **meets 1 or more** exclusion criterion should not be randomised under any circumstances. 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious AE (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after 30 days. Note: the patient is not eligible for rescreening if he or she fails to meet the inclusion or variability criteria for the 6MWD. Patients must sign a new ICF before rescreening. Patients may only be rescreened once. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented in the eCRF so that its effect on study results, if any, can be assessed.

6 STUDY TREATMENTS

Study treatment is defined as any IPs (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

6.1.1 Investigational products

Table 3 Study treatments

	Dapagliflozin	Placebo
Investigational product name:	Dapagliflozin 10 mg	Matching placebo
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	IP will be provided in bottles (155 tablets per bottle). Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and in accordance with each country's regulatory requirements.	IP will be provided in bottles (155 tablets per bottle). Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and in accordance with each country's regulatory requirements.
Provider	AstraZeneca	AstraZeneca

IP investigational product

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 IP received and any discrepancies are reported and resolved before use of the IP, if appropriate.

Only patients enrolled and randomised in the study may receive IP and only authorised site staff may supply or administer IP.

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

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

The Investigator will retain the returned IP until it is collected for destruction, along with any IP not dispensed. The AstraZeneca 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 AstraZeneca representative or delegate will advise on the appropriate method for destruction of unused IP.

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

6.3 Measures to minimise bias: randomisation and blinding

Withdrawn patients will not be replaced.

All patients will be randomly assigned to IP centrally 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 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 intent-to-treat analysis.

The IxRS will provide the Investigator with the kit identification number to be allocated to the patient when 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 site.

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 study site should discuss any potential unblinding (excluding emergency situations) with the AstraZeneca study Physician and prior to initiating the unblinding process. The date and reason that the blind was broken must be recorded in the source documentation and eCRF as applicable. 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.

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

6.3.1 Stratification and capping

The recruitment will be monitored continually in order to achieve adequate proportions of patient subpopulations. The IxRS will be programmed to automatically send alerts at predefined levels for both stratification and capping, whilst also allowing manual closure (or re-opening) as necessary.

6.3.1.1 Stratification

Randomisation will be stratified in IxRS based on patients with and without T2DM at the time of randomisation to ensure approximate balance between treatment groups in the proportions of patients with T2DM. Stratification by T2DM status at the time of randomisation is based on:

- Established diagnosis of T2DM (medical history)

OR

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

6.3.1.2 Capping

The intention is to enrol a typical cross-section of patients with HFpEF to the study.

The numbers of patients randomised to IP will be monitored to ensure the following characteristics are appropriately represented in the study, and caps may be applied in IxRS:

- T2DM status: the number of randomised patients with and without T2DM will be monitored in order to ensure a minimum of 30% in each subpopulation. Randomisation may be capped (ie, no more patients can be randomised in a specific subpopulation) if the pre-determined limit is reached.
- LVEF value: the proportion of patients with LVEF above 40% and below 50% will be monitored to ensure a representative proportion in the study.
- Atrial fibrillation/flutter status: the proportion of patients with atrial fibrillation/flutter will be monitored to ensure a representative proportion in the study.

6.4 Treatment compliance

Dispensing of IP to the patient should be recorded in the appropriate sections of the eCRF. Any change from the dosing schedule, dose interruptions and dose discontinuations should be recorded in the eCRF.

Patients will be asked to bring their bottle of tablets of IP to the clinic at all of their visits. At each visit, any patient found to be non-compliant will be counselled on the importance of taking his or her IP as prescribed. The Investigator or delegate will enter the number of returned tablets in the eCRF.

If the patient forgets to bring his or her bottle of IP to Visit 5 (Final visit), or a Visit for early withdrawal from the study, where dosing occurs in the clinic for PK purposes, a new bottle will be dispensed in accordance with the IxRS.

Site personnel are responsible for managing the 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.

Information regarding overdose of IP is given in Section 8.4.3.

6.5 Concomitant therapy

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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrolment or receives during the study must be recorded in the eCRF at the time points listed in the Schedule of Activities (Table 1), along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose, route, and frequency

6.5.1 Prohibited medications

Concomitant treatment (ie, treatment in combination with IP) with open-label SGLT2-inhibitors (eg, dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin, luseogliflozin, and fixed-dose combinations containing these drugs) during the study is prohibited for all patients. Also, in situations where the patient is not on IP, treatment with open-label SGLT2 inhibitors could interfere with the interpretation of the study. If treatment with a SGLT2-inhibitor alone or in combination is deemed essential, IP must be discontinued before that treatment is started.

6.5.2 Background medication

6.5.2.1 Heart failure background standard of care

Dapagliflozin or matching placebo will be added on to the patient's background standard of care therapy for HFpEF.

Patients' background standard of care therapies for HFpEF should be given 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. Each patient is to be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual (with respect to HF symptoms, renal function, blood pressure, and electrolyte status).

Background standard of care therapies will be recorded in the eCRF as concomitant medication.

6.5.2.2 Anti-diabetes background treatment for patients with T2DM

More than 40% of patients with established HF are estimated to have T2DM (Kristensen et al 2016). Therefore, it is expected that a large proportion of patients will have an established T2DM diagnosis when enrolled in this study and that some patients will develop T2DM during the study. Treatment of diabetes should follow established guidelines, such as the glycaemic goals recommended by the American Diabetes Association and the European Association for the Study of Diabetes in their joint Position Statement (Inzucchi et al 2012, Inzucchi et al 2015).

Diabetes medications at baseline and during the study will be recorded in the eCRF. Patients with T2DM at randomisation will continue their T2DM treatment. SGLT2-inhibitors are prohibited (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 anti-diabetic agents. If needed, T2DM treatments may be adjusted at the discretion of the Investigator or diabetes health care provider.

6.5.3 Other concomitant treatment

Other medication (with the exception of those described above), which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.6 Dose modification (not applicable)

6.7 Treatment after the end of the study

Patients will receive their last dose of IP at Visit 5 (Final visit) for PK assessment. 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 Visit 5 (Final visit), at the discretion of the Investigator.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of investigational product

Discontinuation from IP is not the same as a withdrawal from the study. If the patient temporarily or permanently discontinues IP, the patient should remain in the study (ie, continue to participate in scheduled study visits and evaluations) 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 AE 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 (Section 8.3.1.2)
- Positive pregnancy test (discontinue IP and notify Sponsor representative) (Section 8.4.2)
- Patient decision: The patient is at any time free to discontinue treatment, without prejudice to further treatment

Table 1 outlines data to be collected at the time of treatment discontinuation, and 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 (see the Note below), the patient should be evaluated and temporary interruption of IP should be considered. Volume depletion, hypotension, inter-current medical problems and concomitant medications 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 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.

Note: Whether an acute decline in eGFR has occurred is based on the Investigator's judgement. However, the following may be considered: eGFR value has declined ≥50% compared with baseline or a doubling of serum creatinine compared to the most recent measurement.

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 should be 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 (eg, gastroenteritis, gastrointestinal haemorrhage), or those undergoing major surgery.

7.1.2 Rechallenge

Patients who have temporarily discontinued IP can resume treatment as soon as, in the opinion of the Investigator, the patient's condition is stable and the patient wishes to resume. No minimum time period is necessary before treatment can resume.

7.1.3 Procedures for discontinuation of investigational product

The Investigator should instruct the patient to contact the site before or at the time if IP is stopped. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. The date of last intake IP should be documented in the eCRF. All IP should be returned by the patient at his/her 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 affect 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 study visits in-person, 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.

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 is unable to be contacted by the study site. 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/cell 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 the patient's immediate family, by eg, 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. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (IP and assessments) at his/her own request, 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. Discontinuation of IP in itself is not considered withdrawal of consent.

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

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.

If a patient withdraws from the study, he or she may request destruction of any samples taken, and the Investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up patients as medically indicated.

If a patient withdraws from participation in the study, then his or her enrolment and randomisation codes cannot be reused. Withdrawn patients will not be replaced.

If applicable, the patient will return any wearable activity monitors (accelerometers) that were provided for use at home.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at study closure from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study closure in all patients is crucial for the integrity of the study.

Data to be collected at the time of withdrawal from the study and any further evaluations that need to be completed are listed in Table 1. All IP should be returned by the patient.

7.4 Discontinuation of the study

The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant,
- Are assessed as causally related to IP, and
- Are not considered to be consistent with continuation of the study

Regardless of the reasons for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF.

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

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timings are summarised in the Schedule of Activities (Table 1).

The web-based data capture 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 ensures the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRF. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the patient should continue or discontinue IP.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 1), is essential and required for study conduct.

The maximum amount of blood scheduled to be collected from each patient over the duration of the study, excluding any extra assessments that may be required, will not exceed 28 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Enrolment period

Visit 1, Enrolment (Week -2; Day -14 ± 7)

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 and obtained before signing of the ICF may be used for screening or baseline purposes, provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Table 1).

At Visit 1 (Enrolment), the following procedures and assessments will be completed:

- The patient will sign the ICF.
  - Patients who agree to blood sampling for genetic research must sign the genetic component of the form.
- The Investigator will review the inclusion and exclusion criteria and assign the enrolment number using IxRS.
- Demography, surgical and medical history (including prior cardiac imaging assessments, including echocardiogram and magnetic resonance imaging if required) and concomitant medications will be recorded.
- The following PROs will be administered and must be completed before any further assessments are administered after signing the ICF:
  - KCCQ
  - PGIS in HF symptoms
  - Dyspnoea and fatigue
  - European Quality of Life 5-dimensional, 5-level health status questionnaire (EQ-5D-5L)
- A physical examination will be conducted.
- NYHA Functional Classification will be evaluated and recorded.
- 12-lead electrocardiogram (ECG) will be recorded.
- Systolic and diastolic blood pressure and pulse rate will be measured and recorded.
- Body weight, height and waist circumference will be assessed and recorded.
- The patient will do the 6MWT. This includes administering a suite of assessments: seated pulse rate, blood pressure, oxygen saturation and the Borg CR10 Scale® for dyspnoea and fatigue immediately before doing the 6MWT and again immediately after completing the 6MWT. At selected sites a subset of patients will wear an accelerometer (for use in the clinic only: wearable activity monitor A) while they perform the 6MWT. If the 6MWD is outside the range of ≥100 metres and ≤425 metres the patient is **NOT** eligible for inclusion **OR** rescreening in the study, and will, thus, be considered a screen failure.
- Blood samples will be collected for the following efficacy and safety assessments: NT-proBNP, sodium, potassium, creatinine (for calculation of eGFR), haematocrit and HbA1c, which will all be carried out at a central laboratory. All laboratory values will be available to the study sites and to the Sponsor for this initial screening sample, after which, at subsequent study visits, the values for NT-proBNP and HbA1c will be blinded.
- Urine pregnancy test (beta-human chorionic gonadotropin [β-hCG]) will be conducted (for female patients of child-bearing potential only). The pregnancy test will be performed locally, using a dipstick provided by the central laboratory.
- If applicable, the patient will be given the first wearable activity monitor to take home and he or she will be instructed on how to use it.

- SAEs will be recorded.

Treatment period

Visit 2, Randomisation (Day 1)

Randomisation may occur at Visit 2a (Randomisation A) or Visit 2b (Randomisation B) depending on the outcome of the 6MWT at Visit 2a. If certain criteria are met, patients may be retested for the 6MWT at Visit 2b (Randomisation B) if the 6MWD recorded at Visit 2a (Randomisation A) does not result in exclusion from the study, but also does not permit their inclusion at Visit 2a (Randomisation A).

Before Visit 2a (Randomisation A), the Investigator will assess eligibility based on the central laboratory assessments from Visit 1 (Enrolment). Patients not eligible will be considered screen failures and should not continue to complete Visit 2a (Randomisation A), and they should also return the wearable device (the accelerometer: wearable activity device B #1).

At Visit 2a (Randomisation A), the following assessments and procedures will be completed:

- The Investigator will review all of the inclusion and exclusion criteria to confirm the patient continues to be eligible to participate in the study.
- The following PROs will be administered and must be completed before any further assessments are administered:
  - KCCQ
  - PGIS in HF symptoms
  - Dyspnoea and fatigue
  - EQ-5D-5L
- Changes in surgical and medical history (including cardiac imaging assessments including echocardiogram and magnetic resonance imaging if required) and concomitant medications will be reviewed and recorded.
- A physical examination will be conducted.
- NYHA Functional Classification will be evaluated and recorded.
- Systolic and diastolic blood pressure and pulse rate will be measured and recorded.
- Body weight and waist circumference will be assessed and recorded.
- The patient will do the 6MWT. This includes administering a suite of assessments: seated pulse rate, blood pressure, oxygen saturation and the Borg CR10 Scale® for dyspnoea and fatigue immediately before doing the 6MWT and again immediately after completing the 6MWT. At selected sites a subset of patients will wear an accelerometer (for use in the clinic only: wearable activity monitor A) while they perform the 6MWT.
  - If the 6MWD is outside the range of ≥100 metres and ≤425 metres, the patient is **NOT** eligible for inclusion **OR** rescreening in the study, and will, thus, be considered a screen failure.

- If the 6MWD at Visit 2a (Randomisation A) is within the range of ≥100 metres and ≤425 metres, and the 6MWD recorded at Visit 1 (Enrolment) is within ±15% of the 6MWD recorded at Visit 2a (Randomisation A), the patient can be randomised with the rest of the assessments at Visit 2a being completed.
- If the 6MWD recorded at Visit 1 (Enrolment) is not within ±15% of the 6MWD recorded at Visit 2a (Randomisation A) the patient must stop Visit 2a (Randomisation A) immediately, but may be rescheduled for a third 6MWT within 1 week at Visit 2b (Randomisation B).

Note: Visit 2b (Randomisation B) is completed in exactly the same manner as Visit 2a (Randomisation A) starting with the PRO assessments, followed by recording any changes in surgical and medical history, and concomitant medications; conducting a physical examination; evaluating and recording NYHA Functional Classification; measuring and recording blood pressure and pulse rate; and assessing and recording body weight and waist circumference, then:

- If the 6MWD is outside the range of ≥100 metres and ≤425 metres, the patient is **NOT** eligible for inclusion **OR** rescreening in the study, and will, thus, be considered a screen failure.
- If the 6MWD at Visit 2b (Randomisation B) is within the range of ≥100 metres and ≤425 metres, and the 6MWD recorded at Visit 2a (Randomisation A) is within ±15% of the 6MWD recorded at Visit 2b (Randomisation B), the patient can be randomised with the rest of the assessments at Visit 2b (Randomisation B) being completed.
- If the 6MWD recorded at Visit 2a (Randomisation A) is not within ±15% of the 6MWD recorded at Visit 2b (Randomisation B), the patient must stop Visit 2b (Randomisation B) immediately, is not included or eligible for rescreening and is considered a screen failure.

- Blood samples will be collected for the following efficacy or safety assessments: NT-proBNP, sodium, potassium, creatinine (for calculation of eGFR), haematocrit and HbA1c, which will all be carried out at a central laboratory. All laboratory values will be available to the study sites and to the Sponsor with the exception of NT-proBNP and HbA1c, which will be blinded after the initial screening sample.
- Urine pregnancy test (beta-human chorionic gonadotropin [β-hCG]) will be conducted (for female patients of child-bearing potential only). The pregnancy test will be performed locally, using a dipstick provided by the central laboratory.
- The patient will be randomised to a treatment group (10 mg dapagliflozin or matching placebo in a 1:1 ratio) using the IxRS.
- The patient will be dispensed IP, instructed to take the IP in accordance with the protocol without interruptions, and to bring the dispensed bottle to all study visits.
- If the patient has consented to sampling for genetic research, a blood sample will be collected.

- The patient will take his or her IP in the clinic for PK assessment. The time of dosing will be recorded in the eCRF.
- A blood sample will be collected for a single, post-dose PK assessment (taken between 30 minutes and 4 hours after dosing in the clinic). The time of blood sample collection will be recorded in the eCRF.
- If applicable, the first wearable activity monitor that was administered for use at home will be collected.
- AEs will be recorded.

Visit 3 (Week 8; Day 56 [± 7])

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

- The following PROs will be administered:
  - KCCQ
  - PGIS in HF symptoms
  - PGIC in HF symptoms
  - PGIC in walking ability
  - Dyspnoea and fatigue
  - OTB
- Changes in concomitant medications will be reviewed and recorded.
- Physical examination will be conducted.
- NYHA Functional Classification will be evaluated and recorded.
- Systolic and diastolic blood pressure and pulse rate will be measured and recorded.
- Body weight and waist circumference will be assessed and recorded.
- The patient will do the 6MWT. This includes administering a suite of assessments: seated pulse rate, blood pressure, oxygen saturation and the Borg CR10 Scale® for both dyspnoea and fatigue immediately before doing the 6MWT and again immediately after completing the 6MWT. At selected sites a subset of patients will wear an accelerometer (for use in the clinic only: wearable activity monitor A) while they perform the 6MWT.
- Blood samples will be collected for the following efficacy or safety assessments: NT-proBNP, sodium, potassium, creatinine (for calculation of eGFR), haematocrit and HbA1c, which will all be carried out at a central laboratory. All laboratory values will be available to the study sites and to the Sponsor with the exception of NT-proBNP and HbA1c, which will be blinded after the initial screening sample.
- If applicable, the second wearable activity monitor (wearable activity monitor B #2) will be dispensed for immediate use at home, and the third wearable activity monitor (wearable activity monitor B #3) will be dispensed for delayed use at home, starting at Week 14.
- The numbers of used and unused tablets will be recorded and IP compliance will be checked and the same bottle will be given back to the patient.

- AEs will be recorded.

Visit 4 (Week 14; Day 98 [± 7])

A telephone visit will be conducted at Week 14 for the following tasks:

- For those patients using wearable activity monitors at home, the patient will be reminded to wear the third activity monitor at home starting at Week 14, and to return the second and third monitors at Visit 5 (Final visit).
- The patient will be reminded to attend the next study visit having not taken his or her IP at home on that day, as IP will be taken in the clinic instead, and that the patient needs to bring the IP bottle with them.
- Changes in concomitant medications will be recorded.
- AEs will be recorded.

In exceptional cases, for the patient's convenience, it is allowed to conduct this visit on-site.

Visit 5 (Final visit) (Week 16; Day 116 [± 7])

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

- The following PROs will be administered:
  - KCCQ
  - PGIS in HF symptoms
  - PGIC in HF symptoms
  - PGIC in walking ability
  - Dyspnoea and fatigue
  - EQ-5D-5L
  - OTB
- Changes in concomitant medications will be reviewed and recorded.
- A physical examination will be conducted.
- NYHA Functional Classification will be evaluated and recorded.
- Systolic and diastolic blood pressure and pulse rate will be measured and recorded.
- Body weight and waist circumference will be assessed and recorded.
- The patient will do the 6MWT. This includes administering a suite of assessments: seated pulse rate, blood pressure, oxygen saturation and the Borg CR10 Scale® for both dyspnoea and fatigue immediately before doing the 6MWT and again immediately after completing the 6MWT. At selected sites a subset of patients will wear an accelerometer (for use in the clinic only: wearable activity monitor A) while they perform the 6MWT.
- Blood samples will be collected for the following efficacy or safety assessments: NT-proBNP, sodium, potassium, creatinine (for calculation of eGFR),

haematocrit and HbA1c, which will all be carried out at a central laboratory. All laboratory values will be available to the study sites and to the Sponsor with the exception of NT-proBNP and HbA1c, which will be blinded after the initial screening sample.

- The patient will take his or her IP in the clinic for PK assessment. The time of dosing will be recorded in the eCRF.
- A blood sample will be collected for a single, post-dose PK assessment (taken between 30 minutes and 4 hours after dosing in the clinic). The time of blood sample collection will be recorded in the eCRF.
- If applicable, the second and third wearable (wearable activity monitors B #2 and #3) activity monitors that were administered for use at home will be collected.
- The numbers of used and unused tablets will be recorded and IP compliance will be checked.
- AEs will be recorded.

Visit for early withdrawal from the study

As far as possible, all assessments planned for the Study Closure Visit (Visit 5) should be performed at an Early Withdrawal Visit. At a minimum, safety assessments, PROs, and the 6MWT (if the patient is able) should be performed. It should be noted that this visit is ONLY for patients who choose to leave the study early and, by extension, discontinue study medication.

The following assessments and procedures will be completed, where possible:

- The following PROs will be administered:
  - KCCQ
  - PGIS in HF symptoms
  - PGIC in HF symptoms
  - PGIC in walking ability
  - Dyspnoea and fatigue
  - EQ-5D-5L
  - OTB
- Changes in concomitant medications will be reviewed and recorded.
- A physical examination will be conducted.
- NYHA Functional Classification will be evaluated and recorded.
- Systolic and diastolic blood pressure and pulse rate will be measured and recorded.
- Body weight and waist circumference will be assessed and recorded.
- The patient will do the 6MWT. This includes administering a suite of assessments: seated pulse rate, blood pressure, oxygen saturation and the Borg CR10 Scale® for both dyspnoea and fatigue immediately before doing the 6MWT and again immediately after

completing the 6MWT. A subset of patients will wear an accelerometer (for use in the clinic only) while they perform the 6MWT.

- Blood samples will be collected for the following efficacy or safety assessments: NT-proBNP, sodium, potassium, creatinine (for calculation of eGFR), haematocrit and HbA1c, which will all be carried out at a central laboratory. All laboratory values will be available to the study sites and to the Sponsor with the exception of NT-proBNP and HbA1c, which will be blinded after the initial screening sample.
- The patient will take his or her IP in the clinic for PK assessment. The time of dosing will be recorded in the eCRF.
- A blood sample will be collected for a single, post-dose PK assessment (taken between 30 minutes and 4 hours after dosing in the clinic). The time of blood sample collection will be recorded in the eCRF.
- If applicable, any wearable activity monitors that were administered for use at home will be collected.
- The numbers of used and unused tablets will be recorded and IP compliance will be checked.
- AEs will be recorded.

Visit for early treatment discontinuation

As far as possible, all assessments planned for Visit 5 (Final visit) should be performed at an Early Treatment Discontinuation Visit. At a minimum, safety assessments, PROs, and the 6MWT (if the patient is able) should be performed. It should be noted that this visit is ONLY for patients who choose to discontinue treatment early, but who remain in the study (ie, continue attending study visits and completing study assessments).

The following assessments and procedures will be completed, where possible:

- The following PROs will be administered:
  - KCCQ
  - PGIS in HF symptoms
  - PGIC in HF symptoms
  - PGIC in walking ability
  - Dyspnoea and fatigue
  - EQ-5D-5L
  - OTB
- Changes in concomitant medications will be reviewed and recorded.
- A physical examination will be conducted.
- NYHA Functional Classification will be evaluated and recorded.
- Systolic and diastolic blood pressure and pulse rate will be measured and recorded.

- Body weight and waist circumference will be assessed and recorded.
- The patient will do the 6MWT. This includes administering a suite of assessments: seated pulse rate, blood pressure, oxygen saturation and Borg CR10 Scale® for both dyspnoea and fatigue immediately before doing the 6MWT and again immediately after completing the 6MWT. A subset of patients will wear an accelerometer (for use in the clinic only) while they perform the 6MWT.
- Blood samples will be collected for the following efficacy or safety assessments: NT-proBNP, sodium, potassium, creatinine (for calculation of eGFR), haematocrit and HbA1c, which will all be carried out at a central laboratory. All laboratory values will be available to the study sites and to the Sponsor with the exception of NT-proBNP and HbA1c, which will be blinded after the initial screening sample.
- If applicable, any wearable activity monitors that were administered for use at home will be collected.
- The numbers of used and unused tablets will be recorded and IP compliance will be checked.
- AEs will be recorded.

Unscheduled visit

An unscheduled visit may be performed at any time after randomisation, if required in the opinion of the Investigator where the following assessment will be completed:

- AEs will be recorded.

8.1 Efficacy assessments

8.1.1 Clinical outcome assessment

A clinical outcome assessment is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. The following clinical outcome assessments will be used in this study:

- Performance outcome (PerfO) (Section 8.1.1.1)
- PRO (Section 8.1.1.2)

A PerfO is based on a task performed by a patient according to instructions administered by a health care professional. The PerfO in this study will be the 6MWD. A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation from anyone else. PROs have become an essential endpoint when evaluating benefit/risk of treatments in clinical studies. The following PROs will be used in this study:

- KCCQ
- PGIS in HF symptoms

- PGIC in HF symptoms
- PGIC in walking ability
- Dyspnoea and fatigue
- EQ-5D-5L
- OTB
- Borg CR10 Scale®

8.1.1.1 6MWD

One of the primary efficacy variables used in this study is the 6MWD (used to measure change in exercise capacity). The 6MWD will be measured at the 6MWT, conducted at the time points specified in Table 1.

The 6MWD will be measured based on the American Thoracic Society (ATS) guidelines (American Thoracic Society 2002).

First, patient pulse rate, blood pressure, and oxygen saturation are recorded. Then, immediately before starting the 6MWT, the patient will stand and, using the Borg CR10 Scale® (Section 8.1.1.2 and Appendix P), assess his or her perceived level of dyspnoea and fatigue before exertion.

At selected sites, a subset of at least 100 patients will wear an activity monitor (Monitor A) during the 6MWT. The wearable activity monitor will be distinct from the activity monitors some patients will be given to wear at home. The activity monitors worn during the 6MWT will be for use in the clinic only. Data collected by the wearable activity monitors will be uploaded to the vendor's server and then provided to the sponsor. Data collected by the wearable activity monitors will not be shown to the patient or investigator. The instructions for using the wearable activity monitors will be provided in a separate document.

After completing the Borg CR10 Scale®, the patient will walk as far as he or she can in 6 minutes. The 6MWD will be assessed under standard test conditions, in accordance with the ATS guidelines. Whenever possible, the same person will conduct the 6MWT at each visit. The distance walked (metres) will be measured manually and recorded on paper before being transferred to the eCRF.

Immediately after completing the 6MWT, the patient will use the Borg CR10 Scale® again to reassess his or her perceived level of dyspnoea and fatigue following exertion. Finally, patient pulse rate, blood pressure, and oxygen saturation will again be recorded.

A number of measures have been introduced to minimise variability in patient performance of the 6MWT. Prior to initiating testing, every effort should be made by the Investigator to establish that the patient is in their "usual" state of health: meaning that the patient has no

concurrent medical issues (eg, upper respiratory infection, COPD/chronic HF exacerbation, exacerbation of musculoskeletal difficulties, etc) that might adversely affect his or her performance of the 6MWT. In the event that such conditions are present, the test should be aborted and rescheduled within a 14 day window, to allow time for the resolution of the acute medical issue and the patient to return to his or her "usual" state of health.

For both 6MWD and other variables measured as part of the 6MWT, the value recorded at Visit 2a (Randomisation A) will be the baseline value, except for patients who were successfully retested for the 6MWT, where it will be the Visit 2b (Randomisation B) value.

8.1.1.2 Patient-reported outcomes

PROs are described individually in the following sections.

The PGIC in walking ability and the Borg CR10 Scale® are administered and recorded on paper separately from the other PROs (the KCCQ, PGIS in HF symptoms, PGIC in HF symptoms, Dyspnoea and Fatigue, EQ-5D-5L, and OTB; the results of these are recorded on a site-based electronic tablet by the patient and are termed ePROs). The PGIC in walking ability will be recorded by the patient on paper. The Borg CR10 Scale® forms part of the suite of assessments that are performed before and after the 6MWT (Section 8.1.1.1).

The ePROs are administered and recorded as follows: Patients will perform the ePRO assessments using a site-based electronic tablet during clinic visits at the time points given in Table 1 before the 6MWT. The ePRO assessments must be completed by the patient as soon as he/she arrives at the study site and will take approximately 10 minutes to complete.

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 that site staff follow the Schedule of Activities (Table 1) and make sure the device is set up properly (including using the appropriate time zone), charged, and fully functional at all times in order to minimise missing data.

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

- Patients must not receive help from relatives, friends, or site personnel to answer or clarify the PRO questionnaires, in order to avoid bias.
- The PRO questionnaires must be completed before any other study procedures are conducted at a given visit.
- The PRO questionnaires must be completed before being seen by the Investigator.
- The 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 or her own speed.

Kansas City Cardiomyopathy Questionnaire

Two of the primary efficacy variables are based on the KCCQ (provided in Appendix H), used to assess HF symptoms and physical limitation.

The values recorded at Visit 2a (Randomisation A) will be the baseline values, except for patients who were successfully retested for the 6MWT, where values recorded at Visit 2b (Randomisation B) will be the baseline values.

The 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 measure the patient's perception of their health status independently, which includes HF-related symptoms (frequency, severity and recent change), impact on physical and social function, self-efficacy and knowledge, and how the patients' HF affects their quality of life. Summary scores and domain scores are transformed to a range of 0 to 100. Higher scores represent a better outcome.

Patient global impression of severity in heart failure symptoms

The PGIS (provided in Appendix I) item assesses how a patient perceives his or her overall current severity of HF symptoms. Patients will choose from 6 response options ranging from 'no symptoms' to 'very severe.'

The values recorded at Visit 2a (Randomisation A) will be the baseline values, except for patients who were successfully retested for the 6MWT, where values recorded at Visit 2b (Randomisation B) will be the baseline values.

Patient global impression of change in heart failure symptoms

The PGIC (provided in Appendix J) item assesses how a patient perceives his or her overall change in HF symptoms since the start of the study. Patients will choose from 7 response options ranging from 'much better' to 'much worse.'

Patient global impression of change in walking ability

The PGIC (provided in Appendix K) item assesses how a patient perceives his or her overall change in walking ability since the start of the study. Patients will choose from 7 response options ranging from 'much better' to 'much worse.'

Dyspnoea and fatigue

The dyspnoea and fatigue (provided in Appendix L and Appendix M, respectively) items are single questions, each asking the patient to rate his or her shortness of breath and fatigue, respectively, on a scale from 0 to 10.

The values recorded at Visit 2a (Randomisation A) will be the baseline values, except for patients who were successfully retested for the 6MWT, where values recorded at Visit 2b (Randomisation B) will be the baseline values.

EQ-5D-5L

The EQ-5D-5L (provided in Appendix N) is a self-reported questionnaire that is used to derive a standardised 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.

The values recorded at Visit 2a (Randomisation A) will be the baseline values, except for patients who were successfully retested for the 6MWT, where values recorded at Visit 2b (Randomisation B) will be the baseline values.

Overall treatment benefit

This item (provided in Appendix O) consists of 2 questions measuring the patient's rating of treatment benefit. The first question assesses the patient's impression of the benefits relative to the negative effects. The second question assesses whether the patient would elect to continue the treatment after the end of the study if it were an option.

Borg CR10 Scale®

The Borg CR10 Scale® (provided in Appendix P) is a non-linear scale, ranging from 0 ('nothing at all') to an un-numbered maximum ('absolute maximum; highest possible'), that is used to measure a patient's self-assessment of his or her dyspnoea and fatigue immediately before and immediately after each 6MWT. The results will be recorded by site staff first onto paper before transfer into the CRF (Borg 2007).

8.1.2 Oxygen saturation

Oxygen saturation forms part of the suite of assessments administered during the 6MWT (Section 8.1.1.1) and will be recorded at the time points given in Table 1. Oxygen saturation

will be assessed using a standard pulse oximetry device in a sitting position before and after the 6MWT.

The Visit 2a (Randomisation A) results will be the baseline values, except for patients who were successfully retested for the 6MWT, where values recorded at the Visit 2b (Randomisation B) will be the baseline values.

8.1.3 Physical activity measured at home (accelerometer, Monitor B)

A subset of at least 100 patients (in predefined countries; the countries will be informed if they will participate or not) will receive wearable activity monitors (Monitor B) to wear at home for 3 periods of 7 days as shown in Table 1. Patients will be instructed to wear their activity monitor for as long as possible (ideally 24 hours per day for 7 days). The purpose of wearing the monitors is to assess the total time spent in light to vigorous physical activity (secondary efficacy endpoint), and the changes in the amount, duration and intensity of physical activity parameters (exploratory endpoints) from Visit 1 (Enrolment) at Visit 5 (Final visit; Week 16). Patients will return all of their activity monitors to the site staff.

Data collected by the wearable activity monitors will be uploaded to the vendor's server and will be provided to the Sponsor. Data collected by the wearable activity monitors will not be shown to the patients or the investigators. The specific activity monitor endpoints and their analysis are described in the SAP.

Summary data recorded during 7 days from Visit 1 (Enrolment) to Visit 2a (Randomisation A) will form the baseline values for endpoints derived from the wearable activity monitor worn at home (Monitor B).

8.1.4 Serum NT-proBNP

Blood samples for serum NT-proBNP assessment will be collected at the time points given in Table 1. Serum NT-proBNP will be assessed by the central laboratory and post-screening results will be blinded to all staff associated with conducting the study. There are no plans or processes available to share the blinded data at a later stage (eg, after database lock) and, in effect, the data will remain permanently blinded for the study sites, while they will be available unblinded to the Sponsor after database lock.

The Visit 2a (Randomisation A) result will be the baseline value, except for patients who were successfully retested for the 6MWT, where values recorded at Visit 2b (Randomisation B) will be the baseline value.

8.1.5 New York Heart Association Functional Classification

NYHA Functional Classification (provided in Appendix Q) will be assessed by the Investigators at the time points given in Table 1 and results will be recorded in the eCRF.

The value recorded at Visit 2a (Randomisation A) will be the baseline value, except for patients who were successfully retested for the 6MWT, where values recorded at Visit 2b (Randomisation B) will be the baseline value.

8.2 Safety assessments

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

8.2.1 Physical examination

A physical examination will be performed at the time points specified in Table 1 and include an assessment of general appearance, respiratory and cardiovascular systems (including oedema) and abdomen. Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs (Section 8.3.7).

Physical examination findings will be recorded in the eCRF.

8.2.2 Electrocardiograms

A 12-lead ECG will be performed at Visit 1 (Enrolment); the rhythm will be recorded in the eCRF.

8.2.3 Vital signs

Systolic and diastolic blood pressure and pulse rate will be performed at the time points specified in Table 1 and all results will be recorded in the eCRF.

The measurements should be done before any blood sampling or the 6MWT. 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 patient in a quiet setting without distractions (eg, television, mobile/cell phones).

It should be noted that both blood pressure and pulse rate form part of the suite of assessments that are administered as part of the 6MWT (Section 8.1.1.1). Ideally, both measurements should be taken 3 times at a site visit: once for vital signs, then again before and after the 6MWT. However, as all of these measurements are taken in a sitting position, at the Investigator's discretion, the blood pressure and pulse rate values taken for vital signs can be used for the values before the 6MWT.

8.2.4 Body weight, height and waist circumference

Body weight, height and waist circumference will be assessed at the time points specified in Table 1 and results will be recorded in the eCRF. The patient's body weight, height and waist circumference will be measured with light clothing and no shoes. If the patient has a prosthetic limb, this should be worn consistently during all weight measurements.

8.2.5 Clinical safety laboratory assessments

The following clinical safety laboratory assessments (non-fasting) will be performed at the time points specified in Table 1:

- Sodium
- Potassium
- Creatinine (for calculation of eGFR using the CKD-EPI equation [Levey at al 2009]):
  - $GFR=141x\ \min(S_{cr}/\kappa, 1)^{\alpha}\ x\ \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

Where:

- S_{cr} is serum creatinine in mg/dL,
- κ is 0.7 for females and 0.9 for males,
- α is -0.329 for females and -0.411 for males,
- min indicates the minimum of S_{cr}/κ or 1, and
- max indicates the maximum of S_{cr}/κ or 1

The equation does not require weight because the results are reported normalised to 1.73 m² body surface area, which is an accepted average adult surface area.

- Haematocrit
- HbA1c

Clinical laboratory samples will be analysed at a central laboratory and post-screening results will be available to the study sites and to the Sponsor with the exception of HbA1c, which will be blinded while the trial is being conducted. There are no plans or processes available to share the blinded data at a later stage (eg, after database lock) and, in effect, the data will remain permanently blinded for the study sites, while they will be available unblinded to the Sponsor.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the study site as source data for laboratory variables.

Information on how AEs based on laboratory test results should be recorded and reported is given in Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

8.2.6 Other safety assessments

Patients at risk of volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should have careful monitoring of their volume status, as judged by the investigator.

8.3 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

AEs 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 an AE, SAE, AE leading to discontinuation of IP (DAE), AE leading to amputation or an event potentially placing the patient at risk for a lower limb amputation (preceding events). Information on how to follow up AEs is given in Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs, 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 AEs, SAEs and DAEs, amputations, 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 (Appendix B 2) the site is to record and report these events to the Sponsor or designee within timelines described in Section 8.3.2.

8.3.1.1 AEs leading to amputation, and potential risk-factor AEs for amputations affecting lower limbs ('preceding events')

AEs leading to amputation and potential risk-factor AEs for amputations affecting lower limbs ('preceding events') will be included as AEs of special interest in this study. To ensure that data on amputations are collected systematically, amputations and underlying conditions relevant to amputation will be recorded on a specific eCRF page. The AE leading to amputation should be recorded in the eCRF as an AE or SAE.

Events potentially placing the patient at risk for a lower limb amputation ("preceding events") should also be recorded in the eCRF as an AE or SAE whether or not an amputation has taken place. These will be collected on a dedicated eCRF page.

8.3.1.2 DKA events

For events of Diabetic Ketoacidosis (DKA - see definition below) reported in this study, additional information will be recorded on a specific eCRF page in addition to the AE/SAE form.

DKA events will not be adjudicated in this study.

DKA definition:

A diagnosis of DKA should only be made in a clinical setting consistent with DKA (based on patient history, symptoms, and physical examination) 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 urinesticks).

AND

- At least 1 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

8.3.1.3 Capture of additional laboratory values

Any additional safety laboratory assessments during the study period, including creatinine, will be obtained according to 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, in accordance with the Investigator's judgment.

8.3.2 Time period and frequency for collecting AE and SAE information

Non-serious AEs will be collected from the time of randomisation until the end of Visit 5 (Final visit). SAEs will be collected from the time of signing the ICF until the end of the Visit 5 (Final 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 them being available.

Investigators are not obligated to seek AE or SAE actively in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he or she considers the event to be reasonably related to the IP or study participation, the Investigator may notify the Sponsor.

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.

8.3.3 Follow-up of AEs and SAEs

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

Any AEs that are unresolved at the patient's last visit 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) or SAE(s) at the end of the study, if judged necessary.

8.3.4 AE data collection

AE data will be collected in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The following variables will be collected for each AE:

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

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- 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)
- Causality assessment to other medication

8.3.5 Causality collection

The Investigator will assess causal relationship between 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 IP?'

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.

8.3.6 AEs based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: '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. 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.

8.3.7 AEs based on examinations and tests

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration from baseline in protocol-mandated laboratory values or 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 laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding on physical examination compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.8 Hy's Law

Information relating to Hy's Law is given in Appendix E. Dapagliflozin has an established safety profile; therefore, no liver function tests are planned in this study. The Investigator should be vigilant for cases of Potential Hy's Law cases from ad hoc laboratory tests or AEs. Additional safety samples, for example, liver function tests to determine Potential Hy's Law cases, may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate page of the CRF.

8.3.9 Disease-under study (not applicable)

8.3.10 Disease progression (not applicable)

8.4 Safety reporting and medical management

8.4.1 Reporting of SAEs

All SAEs must 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 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs 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 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the electronic/web-based data capture system, an automated email alert is sent to the designated AstraZeneca representative.

If the electronic/web based data capture 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.

Further guidance on the definition of an SAE is given in Appendix B.

8.4.2 Pregnancy and maternal exposure

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 (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

Women of child-bearing potential who are not using contraception as defined in Section 5.2, Exclusion Criterion 19 are not allowed to be included in this study. Should a pregnancy still occur, the IP 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, IP should be discontinued.

8.4.3 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 T2DM. 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 Investigator's Brochure.

- 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 with 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 an SAE, the standard reporting timelines apply (Section 8.3.2). For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (for Initial Fatal/Life-threatening or follow-up Fatal/Life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication error can be found in Appendix B.

8.5 Pharmacokinetics

At Visit 2a (Randomisation A) (Day 1), or Visit 2b (Randomisation B) (Day 1) as applicable, and Visit 5 (Week 16/Day 116 [± 7]) (or Study Withdrawal Visit, if possible), patients will take their dose of IP in the clinic so that PK can be evaluated. One blood sample (2 mL) will be collected from each patient no earlier than 30 minutes after dosing and no later than 4 hours after dosing.

The purpose of the PK assessment is to explore the exposure-response relationship for efficacy and safety endpoints. Results will be reported separately from the clinical study report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.1 Determination of drug concentration

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

8.5.2 Storage and destruction of pharmacokinetic samples

PK samples will be disposed of after the Bioanalytical Report is finalised or 6 months after the draft Bioanalytical Report (whichever is earlier) is issued, unless requested for future analyses.

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

8.6 Pharmacodynamics (not applicable)

8.7 Genetics

Genetic testing is not evaluated in this study. However, a blood sample will be collected for future exploratory genetic evaluation from patients who have provided separate informed consent specifically for genetic evaluation. Results will be reported separately from the results of this study.

8.7.1 Collection of mandatory genetic samples (not applicable)

8.7.2 Optional exploratory genetic sample

Approximately 6 mL blood will be collected for DNA isolation from patients who have consented to participate in future exploratory genetic evaluations. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

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

8.7.3 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or in accordance with local regulations from the date of the patient's last visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the DNA.

8.8 Biomarkers (not applicable)

8.9 Health economics (not applicable)

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives using the statistical analytical software, SAS.

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

A comprehensive SAP will preferably be prepared and approved before the first patient is randomised, and any subsequent amendments will be documented, with final amendments completed prior to database lock and study unblinding.

9.1 Statistical hypotheses

The primary objectives of this study are to demonstrate superiority of dapagliflozin (Active treatment) over placebo (Control) in terms of KCCQ-TSS, KCCQ-PLS, and 6MWD.

Consequently, the statistical hypotheses used for the family of primary endpoints are the following:

- H0: $\mu(A) = \mu(C)$
  - Versus
- H1: $\mu(A) \neq \mu(C)$

Where H0: and H1: are the null and alternative hypotheses, respectively and μ(A) and μ(C) represent the mean responses among patients receiving Active and Control treatment, respectively.

9.2 Sample size determination

Enrolment in this study is intended to yield approximately 500 patients randomised to treatment. This sample size estimate is based on the primary endpoints, KCCQ-TSS, KCCQ-PLS, and 6MWD, as well as the assumption that mortality over the entire 16-week treatment period is about 5% in each treatment arm.

[redacted]

9.3 Populations for analyses

9.3.1 Enrolled

All patients who sign the ICF will be included in the Enrolled Population.

9.3.2 Full analysis set

All patients representing the study inclusion/exclusion criteria and who have been randomised to IP will be included in the Full Analysis Set (FAS), irrespective of their protocol adherence, addition or modification of background rescue medications, switches to alternative medications, and continued participation in the study. Patients will be analysed according to their randomised IP assignment, irrespective of the treatment they actually received. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

9.3.3 Safety analysis set

All randomised patients who received at least 1 dose of randomised treatment will be included in the Safety Analysis Set. Patients will be analysed according to the treatment actually received. For any patients given incorrect treatment, ie, randomised to one of the treatment

groups, but actually given the other treatment, the treatment group will be allocated as follows: Patients who received both incorrect and correct treatment will be analysed according to their randomised treatment. Patients who received only the incorrect treatment will be analysed according to that treatment.

The Safety analysis set will be considered the primary analysis set for all safety variables.

9.4 Statistical analyses

9.4.1 Efficacy analyses

The primary and secondary efficacy endpoints will be evaluated under a combined treatment policy (intent-to-treat) and composite variable strategy estimand, including differences in the outcome variable at the end of the 16-week treatment period. The intent-to-treat approach is employed to reflect the effect of the initially assigned randomised study drug, irrespective of exposure to study drug, concomitant treatment as well as subsequent treatment after discontinuation of study drug. A composite variable strategy approach is employed to account for deaths occurring during the follow-up period.

9.4.1.1 Analysis of the primary efficacy variables

The primary efficacy endpoints are change from baseline in each of KCCQ-TSS, KCCQ-PLS, and 6MWD at Week 16. Each of these will be analysed based on a rank ANCOVA model with rank-based change from baseline at Week 16 as the outcome. The rank-based baseline value will be included as a covariate along with the stratification factor used in the randomisation; further details are available in the SAP. Ties will be assigned the mean of the corresponding ranks.

In this analysis, data that are missing due to death will be ranked “worse” than observed data and data missing for reasons other than death, and the ranking amongst the deceased patients will be based on last value while alive. Missing data due to reasons other than death (eg, missing visits, early withdrawal from the study, including lost to follow-up) will be replaced by multiple imputation with predictive mean matching. Rank ANCOVA will then be applied to each imputation dataset and results will be pooled. Sensitivity analyses will be performed to assess the robustness of the treatment effect from the handling of missing data and are described in detail in the SAP.

The mean difference in change from baseline 6MWD will also be presented, both as an absolute change and as a percentage of baseline.

The magnitude of treatment effect in KCCQ-TSS and KCCQ-PLS will also be presented as the number and percentage of patients by treatment group across the following categories of change from baseline:

- Death
- Deterioration from baseline (change from baseline ≤-5)
- Stable (-5< change from baseline <5)
- Improvement (change from baseline ≥5)

The magnitude of treatment effect in 6MWD will also be presented as the number and percentage of patients by treatment group in the following categories of change from baseline:

- Death
- No improvement from baseline (change from baseline ≤0 metres)
- Minimal improvement (0< change from baseline <30 metres)
- Improvement (change from baseline ≥30 metres)

Clinical meaningfulness has not been demonstrated for the pre-specified categories. Therefore, thresholds for clinically meaningful within-patient change for KCCQ-TSS, KCCQ-PLS, and 6MWD will be assessed using pre-specified methods described in the SAP and the derived thresholds will be the main categories used to assess the magnitude of treatment effect.

To provide a visual display of the relative benefit of dapagliflozin over placebo across different ranges of response at Week 16, empirical cumulative distribution functions for each treatment group will be presented.

9.4.1.2 Analysis of the secondary efficacy variable

Analysis of endpoints using data retrieved from wearable activity monitors will be performed in the same way as for the primary endpoint family. Sensitivity analysis for the secondary endpoint is described in detail in the SAP.

Change in total time spent in light to vigorous physical activity from baseline to end of study, will be based on wearable activity monitor data collected at baseline and at the end of the 16-week treatment period. Baseline will be measured for all subjects included in the FAS, at sites with wearable devices, over one week, between enrolment (Visit 1) and the first randomisation attempt (Visit 2a). Change from baseline will be measured over one week leading up to Week 16. At each time point, up to seven days of wearable activity monitor data will be analysed. Empirical cumulative distribution functions will be presented to show the individual-level effects across a range of definitions of responders at Week 16. The threshold

for clinically meaningful within-patient change will be evaluated using a completely pre-specified algorithm with anchor-based methods, the details of which are described in the SAP.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data will be summarised descriptively and will not be formally tested. Patients who received IP which is not consistent with the treatment he or she was randomised to receive will also be listed.

The numbers and percentages of patients with AEs, SAEs, DAEs, AEs leading to 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 for pre-specified safety variables using all observations, regardless of whether patients are on or off IP.

Details of the analysis and presentation of data for other safety variables (physical examination findings, systolic and diastolic blood pressure, pulse rate, body weight, and clinical safety laboratory assessments) will be provided in the SAP.

9.4.3 Other analyses

Exploratory analyses, including subgroup analyses, will not be controlled for multiplicity. Details of the analyses planned for the exploratory endpoints (Table 2) and a list of subgroup variables and categories, are described in the SAP.

PK analyses and results will be presented separately from the main clinical study report.

9.4.4 Methods for multiplicity control

The type I error rate will be controlled to support superiority claims for dapagliflozin compared with placebo. The overall type I error (alpha) will initially be split between the KCCQ-TSS, KCCQ-PLS, and 6MWD. Testing will proceed to the secondary endpoint if statistical significance is demonstrated for at least 1 endpoint in the primary endpoint family. The multiplicity testing procedure will be described in detail in the SAP.

9.5 Interim analyses

Given the short duration of the study, an interim analysis will not be performed.

9.5.1 Data monitoring committee

A data monitoring committee will not be used for this study because of the short study duration and the accumulated safety profile of dapagliflozin.

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;11(4):416-27.

American Thoracic Society 2002
American Thoracic Society. ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002;166:111-7.

Borg 2007
Borg G. The Borg CR10 Scale® Folder. A method for measuring intensity of experience. Hasselby Sweden. Borg Perception, 2004, 2007.

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.

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 Metab 2015;17:1180-93.

Comin-Colet et al 2013
Comin-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Luscher TF, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. Eur Heart J 2013;34:30-8.

Cook et al 2014
Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol 2014;171(3):368-76.

DeBock et al 1994
DeBock V, Mets T, Romagnoli M, Derde MP. Captopril treatment of chronic heart failure in the very old. J Gerontol 1994;49:M148–52.

Dreyer et al 2016
Dreyer RP, Jones PG, Kutty S, Spertus JA. Quantifying clinical change: discrepancies between patients' and providers' perspectives. Qual Life Res 2016;25:2213-20.

Ferreira et al 2016
Ferreira JP, Duarte K, Graves TL, Zile MR, Abraham WT, Weaver FA, et al. Natriuretic Peptides, 6-Min Walk Test, and Quality-of-Life Questionnaires as Clinically Meaningful Endpoints in HF Trials. J Am Coll Cardiol 2016;68(24):2690-707.

Filippatos et al 2017
Filippatos G, Maggioni AP, Lam CSP, Pieske-Kraigher E, Butler J, et al. Patient-reported outcomes in the Soluble guanylate Cyclase stimulatoR in heArT failure patientS with PRESERVED ejection fraction (SOCRATES-PRESERVED) study. Eur J Heart Fail 2017;19:782-91.

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;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;3(3):252-9.

Holland et al 2014
Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D et al. An official European Resiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428-46.

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.

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) [published erratum appears in Diabetologia 2013; 56(3):680]. Diabetologia 2012;55(6):1577-96.

Inzucchi et al 2015
Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach.

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–9

Kosiborod et al 2017
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 2016
Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B et al. Risk related to pre–diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail 2016;9:e002560.

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.

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; 377:644-57.

O'Keeffe et al 1998
O'Keeffe ST, Lye M, Donnnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six-minute walk test in elderly heart failure patients. Heart 1998;80:377-82.

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.

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.

Ponikowski et al 2016
Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129-200.

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.

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.

Shoemaker et al 2012
Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Triangulating Clinically Meaningful Change in the Six-minute Walk Test in Individuals with Chronic Heart Failure: A Systematic Review. Cardiopulmonary Phys Ther J 2012;23(3):5-15.

Shoemaker et al 2013
Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically Meaningful Change Estimates for the Six-Minute Walk Test and Daily Activity in Individuals with Chronic Heart Failure. Cardiopulmonary Phys Ther J 2013;24(3):21-9.

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(4):707-15.

Wanner et al 2016
Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016;375(4):323-34.

Zinman et al 2015
Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117-28.

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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, 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.

If a subject declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the subject and he/she will not be excluded from other aspects of the study.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorised designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The subject will give a separate agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will indicate this in the ICF. 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 already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

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

There will not be a data monitoring committee in this study because of the short duration of the study and the accumulated safety profile of dapagliflozin.

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

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 in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

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 eCRF 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 AEs

An AE 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 (eg, 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 SAE

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 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 1of 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 (eg, 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 (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the 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 jeopardise the subject or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

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

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 making an assessment of causality, consider the following factors when deciding whether 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 recognised 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 study drug 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 recognised that could have led to an error

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

- Drug name confusion
- Dispensing error eg, 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 eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, 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 1 of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, 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 AstraZeneca product

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

Appendix C Handling of human biological samples

C 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 AstraZeneca-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 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.

C 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 eg, Ebola, Lassa fever virus:

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

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus 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 D Genetics

D 1 Use/analysis of DNA

Genetic variation may affect 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 affect 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, ie, the entire genome.

The results of genetic analyses may be reported in the clinical study report 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 HF with preserved ejection fraction continues but no longer than 15 years or other period in accordance with 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 declines 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 2a or Visit 2b (Randomisation A or Randomisation B), as applicable. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an 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 1 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 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 patient 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 patient must sign and date both the consent form for the main study and the genetic component of the study. A copy of the signed and dated consent form must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient 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 SAP may be prepared where appropriate.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 ×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

The Investigator will remain vigilant for any local laboratory reports where the identification criteria are met; where this is the case the Investigator will:

- Notify the AstraZeneca representative,
- Request a repeat of the test (new blood draw),
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result.

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AstraZeneca standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

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

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
CKD-EPI	chronic kidney disease epidemiology collaboration (formula)
COPD	chronic obstructive pulmonary disease
(e)CRF	(electronic) case report form
CTCAE	Common Terminology Criteria for Adverse Event
DAE	adverse event leading to discontinuation of investigational product
DKA	diabetic ketoacidosis
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	European Quality of Life 5-dimension, 5-level health status questionnaire
FAS	Full Analysis Set
GCP	Good Clinical Practice
HbA1c	glycated haemoglobin
HF	heart failure
HFpEF	heart failure with preserved left ventricular ejection fraction
HFrEF	heart failure with reduced left ventricular ejection fraction
ICF	informed consent form
ICH	International Conference for Harmonisation
IEC	Independent ethics committee
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.
IRB	Institutional review board
IxRS	interactive voice/web response system
KSSQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
MET	metabolic equivalent of task
MRI	magnetic resonance imaging
6MWD	6-minute walk distance
6MWT	6-minute walk test
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association

Abbreviation or special term	Explanation
OTB	overall treatment benefit
PerfO	Performance outcome
PGIC	patient global impression of change
PGIS	patient global impression of severity
PK	pharmacokinetic
PLS	physical limitation score
(e)PRO	(electronic) patient-reported outcome
QoL	Quality of Life
SAE	serious adverse event
SAP	statistical analysis plan
SGLT2	Sodium-glucose co-transporter-2
T2DM	Type 2 diabetes mellitus
TSS	total symptom score

Appendix H The Kansas City 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 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 I Patient Global Impression of Severity in 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

Appendix J Patient Global Impression of Change in Heart Failure Symptoms

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

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

Appendix K Patient Global Impression of Change in Walking Ability

Overall, how would you rate the change in your walking ability since starting this study?

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

Appendix L Patient Rating of Dyspnoea

Overall, how would you rate your shortness of breath in the past 7 days?

0	1	2	3	4	5	6	7	8	9	10
No shortness of breath										As bad as you can imagine

Appendix M Patient Rating of Fatigue

Overall, how would you rate your fatigue in the past 7 days?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

Appendix N European Quality of Life 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 ❑

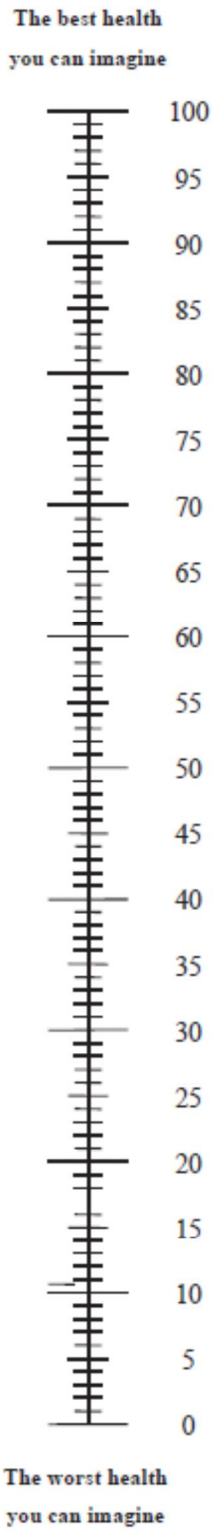
I am moderately anxious or depressed ❑

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 O Patient Overall Treatment Benefit

Thinking about both the positive and negative aspects of the study medication, the benefits of the study medication were:

- **much greater** than the negative effects
- **somewhat greater** than the negative effects
- **equal** to the negative effects
- **somewhat less** than the negative effects
- **much less** than the negative effects

If you had the option, would you continue taking the study medication after the study ends?

- Yes
- Unsure
- No

Appendix P The Borg CR10 Scale®

0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	**Extremely strong**	**"Maximal"**
11		
↯		
●	Absolute maximum	Highest possible

Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

Instruction. Use this rating scale to report how strong your perception is. It can be exertion, pain or something else. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or "Extremely strong", "Maximal" is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is "Very weak", you should say "1", if it is "Moderate", say "3". Note that "Moderate" is "3" and thus weaker than "Medium", "Mean" or "Middle". If the experience is "Strong" or "Heavy" (it feels "Difficult") say "5". Note that "Strong" is about half of "Maximal". If your feeling is "Very strong", choose a number from 6 to 8. If your perception or feeling is stronger than "10", - "Extremely strong", "Maximal" – you can use a larger number, e.g. 12 or still higher (that's why "Absolute maximum" is marked with a dot "•").

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating exertion give a number that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 "Nothing at all", means that you don't feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

1 "Very weak" means a very light exertion. As taking a shorter walk at your own pace.

3 "Moderate" is somewhat but not especially hard. It feels good and not difficult to go on.

5 "Strong". The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as "Maximal".

7 "Very strong" is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

10 "Extremely strong – Maximal" is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

● Is "Absolute maximum" for example "12" or even more.

Any questions?

Borg CR10 scale®
© G. Borg, 1998, 2007
English

At the beginning of the 6MWT the investigator shows the Borg CR10 Scale® to the patient (on paper) and asks the patient: “Please grade your perceived level of shortness of breath using this scale”. Then the investigator asks: “Please grade your perceived level of fatigue using this scale”. At the end of the 6MWT, the investigator reminds the patient of the breathing number that they chose before the exercise and asks the patient to grade their breathing level again. Then the investigator asks the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

Appendix Q New York Heart Association 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.

SIGNATURE PAGE

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