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

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.

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.

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

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.

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.

- 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

- 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.'

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.

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)**		
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]	

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

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.

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

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

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**
❑	❑	❑	❑	❑	❑	❑

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 ❑

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

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

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

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.

- 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.

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.

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

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.

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)**		
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			

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

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.

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 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)	❑	❑	❑	❑	❑	❑

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
❑	❑	❑	❑	❑

- 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 = ☐