Assessments including Working Practice Guidelines (WPG)

	Visit 1 (Screening)	Visit 2	Visit 3 (Baseline)	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	-30 days to -14 days	-7 days +/- 3 days	Day 0	Week 1 +/- 3 days	Week 4 +/- 3 days	Week 10 +/- 3 days	Week 16 +/- 3 days	Week 20 +/-3 days
	Research Site	Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site
Informed Consent	X							
Eligibility	X		X					
Demographics/Medical History	X							
NYHA Class	X						X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Weight	X		X				X	
Height, Waist and hip circumference	X							
Blood Pressure & pulse	X		X				X	
Physical Examination	X						X	
ECG	X							
Echocardiography (LVEF) if not available within 24 months.	X							
Education/Review of Glucose Management and ketones / documentation of glucose and ketone readings / documentation of hypoglycaemic and DKA events		X	X	X	X	X	X	X
Registration with CGM app (if not already signed up), optional		X						
Documentation of summary Data and/or glucose readings from CGM, from previous 2 weeks			X		X		X	
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X		X		X		X	
Diabetes Treatment Satisfaction Questionnaire (status at baseline, change+status at 16-weeks)			X				X	
EQ-5D-5L Questionnaire			X				X	
6 minute-walk test			X				X	
Urine pregnancy test	X		X					
Safety Bloods (FBC, U&E, LFT, glucose)	X		X		X		X	
HbA1c	X						X	
NT-proBNP or BNP (local) within 12 months of screening	X							
Research blood sample (NT-proBNP for central lab analysis in Dundee)			X				X	
Research blood sample (C-peptide for central lab analysis in Dundee)			X					
Urine albumin, creatinine, sodium			X		X		X	
Additional research blood samples			X				X	
Additional research urine samples			X				X	
Randomisation			X					
Dispensing of IMP			X					
Compliance to IMP				X	X	X	X	
IMP Accountability			X				X	

Demographic details

- Record participants age, sex at birth and ethnicity.

Medical History

- Medical History should be completed as fully as possible and should be as diagnosed by a doctor.
- "Other relevant medical history" should include:
  - Medical conditions for which the participant is receiving concomitant medications.
  - Medical conditions which impact on the participant's Activities of Daily Living or ability to complete the trial assessments.
- Abbreviations should not be used.
- Date of diagnosis are not required except for the year of Diabetes diagnosis.
- If applicable, provide dates of most recent hospitalisation for DKAs, hypoglycaemia and heart failure.
- The participant should be assessed by a delegated doctor as to whether they have any unstable co-morbidities which in their opinion would make the participant unsuitable to be enrolled in the trial.

New York Heart Association (NYHA) class

Categorise participants functional status according to their degree of heart failure symptoms using one of the four classes provided below:

Class I - No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea (shortness of breath).

Class II - Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnoea (shortness of breath).

Class III - Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnoea.

Class IV - Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. If any physical activity is undertaken, discomfort increases.

Height WPG

Equipment

- Stadiometer.

Procedure

- Ask the participant to remove their shoes and any bulky clothing (e.g., jacket, coat, cardigan).
- Raise the head plate of the height measure and ask the participant to stand with their feet flat on the centre of the base plate, with their feet together and heels against the rod.
- Their back should be as straight as possible, against the rod but not leaning on it and their arms should be hanging loosely by their side.
- The participant's head should be in a horizontal position.
- Ask the participant to look straight ahead, breathe in deeply and stretch to their fullest height.
- Lower the headplate until it is resting on the participant's head, and then ask them to step forward.
- Record the height to the nearest mm.

Weight WPG

Equipment

- Weighing scale

Procedure

- Ask participant to remove all outer layers of clothing (e.g., jackets, heavy or baggy jumpers, cardigans, or waistcoats) and shoes, and to empty their pockets and remove any heavy jewellery.
- Turn on the weighing scale and wait for the display to read zero.
- Ask the participant to stand still on the scale with both feet flat, hands by their side and head facing forward.
- Once the scales have stabilised, record the reading in kg to the nearest 100 g.

Waist circumference WPG

Equipment

- Flexible tape measure.

Procedure

- Ask the participant to remove all outer layers of clothing (e.g., jackets, heavy or baggy jumpers, cardigans, or waistcoats) to ensure only a thin layer of clothing is present.
- Participant should stand still with arms at the sides, feet together and the abdomen relaxed.
- Using a flexible tape measure waist circumference at the mid-point between the lower margin of the last palpable rib and the top of the iliac crest (i.e. top of the hip), perpendicular to the long axis of the trunk.
- Measurement should be taken at the end of a normal expiration (end tidal) with minimal skin compression and repeated twice. If measurements are within 1 cm of one another, the average of the two should be recorded. If the difference exceeds 1 cm the two measurements should be repeated.

Hip circumference WPG

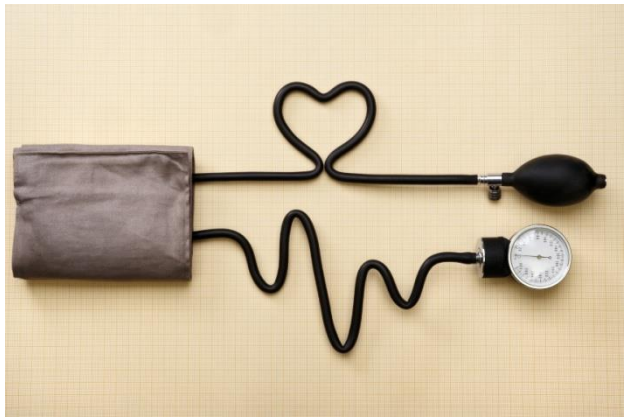
Equipment

- Flexible tape measure.

Procedure

- Participants stand with feet close together, their arms at the side, body weight evenly distributed and with the gluteal muscles relaxed.
- To assess hip circumference, the tape is passed in a horizontal plane across the buttocks at the level of their greatest posterior protuberance (i.e. maximal circumference of the buttocks), perpendicular to the long axis of the trunk.
- Measurement should be repeated twice. If measurements are within 1 cm of one another, the average of the two should be recorded. If the difference exceeds 1 cm the two measurements should be repeated.

Vital Signs WPG



Equipment

- Blood Pressure Monitor

Procedure - Blood Pressure & Pulse

- Select appropriately sized cuff**.**
- Place the cuff directly against the skin, as clothing may cause a faint heartbeat and result in error.
- Ensure that the participant is sitting comfortably in a chair with back support in a quiet room for at least 5-10 minutes before measurement is taken**.**
- Participant should have both feet flat on the floor with the legs uncrossed and arm supported so that the middle of the cuff is at the level of the right atrium.
- Ask the participant not to talk or move during blood pressure measurement. The blood pressure should be taken twice, and the second reading entered in the eCRF.
- Record the readings in the medical records for source data verification (SDV).

Physical Examination

- A detailed physical examination is mandatory at screening to exclude participants with co-morbidities or other clinical disorders that would constitute an exclusion from the trial.

- Should be completed by a delegated doctor and documented in the participant's medical notes as well as on the eCRF.

- Examination needs to include the following systems:
  - Cardiovascular
  - Respiratory
  - Gastrointestinal
  - Neurological

Electrocardiogram (ECG) WPG

Equipment

- ECG Machine

Procedure

- A 12-lead ECG should be performed according to standard guidelines for determination of heart rhythm (sinus or atrial fibrillation or other e.g. paced) at screening.
- Ensure date, patient name, CHI/hospital number and study ID number are printed or written on the ECG.
- A doctor delegated this task on the Delegation Log should review the ECG before randomisation of participant.
- Doctor reviewing ECG should write any abnormal findings and actions taken in patient's medical notes.
- With the patient's consent their GP should be informed of any abnormal findings.
- File ECG in patient's medical notes as source data.

Echocardiogram WPG

Equipment

- Ultrasound device

Procedure

- If an echocardiogram has not been performed within 24 months of screening a 2-dimensional transthoracic echocardiogram should be performed at screening for assessment of the following parameters:
  - LVEF using Simpson's rule.
  - The presence or absence of left atrial enlargement, left ventricular hypertrophy and diastolic dysfunction should be documented.

- If a numerical assessment of LVEF is not available, the following conversion should be used to enter a numerical value for the trial:

Documented LVEF	Numerical LVEF equivalent (%)
Normal/preserved	55
Mildly reduced	50
Mild/moderate	45
Moderate	40
Moderate/severe	35
Severe	30

Review and recording of insulin and blood glucose management, diabetic ketoacidosis and hypoglycaemia (Part 1 of 6)

- Most patients in the UK are provided with CGM systems (e.g. Flash CGM, Dexcom, Guardian) and capillary beta-ketone meters as standard care and these are required to take part in the trial.
- A review of glucose and ketone management should be performed at each trial visit after screening by a local investigator or a delegated appropriately trained member of staff (e.g. Specialist Diabetes Nurse).
- The final decision on management of glycaemic control and ketone management should be taken between the local investigator or delegate and the participant.
- Participants may be provided with medical alerts (e.g. STOP-DKA wallet card or local guidelines), dependent on local investigator's preference.
- Participants should be managed in accordance with the recently developed position statements of the Association of British Clinical Diabetologists (Dashora et al., 2019) and the International Consensus approach (Danne et al., 2019).

Dashora U, et al., Association of British Clinical Diabetologists (ABCD) position statement on the use of sodium-glucose cotransporter-2 inhibitors in type 1 diabetes (updated 2019). Br J Diabetes. 2019:66-72.
Danne T, et al., International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium-Glucose Cotransporter (SGLT) Inhibitors. *Diabetes Care*. 2019;42:1147-1154.

Review and recording of insulin and blood glucose management, diabetic ketoacidosis and hypoglycaemia (Part 2 of 6)

- All participants should be carefully monitored throughout the trial and insulin dose adjustments made under the supervision of the research team.

- Participants will be specifically asked to check their glucose and ketone levels using their CGM and capillary beta-ketone meter as follows:
  - In the 3 days before and after starting trial drug/placebo (i.e. before and after randomisation) participants should check paired glucose and ketone levels 4 times per day (e.g. before each meal and before bedtime), as well as 2 hours after changing each insulin giving set for those on insulin pump therapy. This will allow participants and investigators to obtain an understanding of baseline glucose and ketone levels and the response study drug/placebo.
  - At least once weekly throughout the trial, ideally at the same time of day each week.
  - If feeling unwell.

- Participants may wish to check ketone levels any other time at their discretion or that of the local investigator.

Review and recording of insulin and blood glucose management, diabetic ketoacidosis and hypoglycaemia (Part 3 of 6)

Insulin management

- Once randomisation is complete, individuals with an HbA1c <58mmol/mol at screening should have a 10% insulin dose reduction prior to taking their first dose of sotagliflozin/placebo.
- The 10% reduction in insulin dose should **NOT** be made for those participants with HbA1c ≥58mmol/mol at screening.
- All participants should be advised to monitor blood glucose and ketones regularly after taking their first dose of sotagliflozin/placebo and to adjust insulin doses every 24-48 hours, as required, to achieve recommend blood glucose targets.
- The participants 7-day average total, basal and bolus doses of insulin used should be recorded at screening, randomisation, week 4 and week 16 visits.

Review and recording of insulin and blood glucose management, diabetic ketoacidosis and hypoglycaemia (Part 4 of 6)

Blood glucose management

- Where participants have a compatible CGM they should be asked if they wish to sign-up to free apps such as LibreView (Abbott) or Clarity (Dexcom). Participants create their own account and can download their blood glucose readings then give access to local investigators to view reports to assist with glucose management.
- Participants who do not wish to sign-up to one of these apps will **NOT** be excluded from participating in the trial.
- Investigators should recommend alarm settings on participants CGM to be set at a high alarm of 15 mmol/L (13 mmol/L if on an insulin pump) and a low alarm of 3.9 mmol/L. The lower alarm may be subsequently adjusted based on clinician and participant judgment and preferences. Alarm levels and CGM metrics should be assessed by the local research team at each visit.
- Summary CGM data should be entered into the data management system for the 2 weeks prior to the trial visits at randomisation (i.e. Visit 3), week 4 (i.e. Visit 5) and week 16 (i.e. Visit 7).
- The variables collected will include number of days CGM worn, percentage of time CGM is active, mean blood glucose, glycaemic variability (%CV) and percentage time in target, time above target and time below target.

Review and recording of insulin and blood glucose management, diabetic ketoacidosis and hypoglycaemia (Part 5 of 6)

Diabetic ketoacidosis

- DKA in this trial is defined as: blood ketone >3.0 mmol/l **and** blood pH of <7.3 or a bicarbonate <18mmol/l.
- Participants should be provided with information on how to prevent, recognise, and treat DKA along with educational prompts.
- Participants should be educated about precipitating factors for DKA (e.g. acute medical illness, vomiting, insulin pump failure, excessive carbohydrate restriction, excessive alcohol), when to discontinue therapy if these events occur and provided with contact details of the local research team and relevant emergency contacts for advice should any of these situations occur.
- Participants should be advised to perform additional ketone testing if capillary/CGM glucose is >11.1mmol/L for >2 hours, if feeling sick, if feeling unwell (even if capillary glucose levels are not high), or with changes in diet, activity, insulin dose or events known to precipitate ketoacidosis and follow sick day rules as discussed with local team.
- If blood ketones are ≥0.6 mmol/L the clinician and participant should document reasons (e.g., alcohol, recent illness) for this and how it was managed. Advice should also be given regarding other times to check ketone levels (e.g., guidance is given in STOP-DKA protocol).

Review and recording of insulin and blood glucose management, diabetic ketoacidosis and hypoglycaemia (Part 6 of 6)

Hypoglycaemia

- Hypoglycaemic events during the trial will be defined and documented as:
  - Level 1 hypoglycaemia (mild) - Measured plasma/capillary glucose concentration less than 3.9 mmol/L (70 mg/dL) but greater than or equal to 3.0 mmol/L (54 mg/dL). If CGM having this range for at least 15 min.
  - Level 2 hypoglycaemia (moderate) - Measured plasma/capillary glucose concentration less than 3.0 mmol/L (54 mg/dL). If CGM having this range for at least 15 min.
  - Level 3 hypoglycaemia (severe) - An event requiring hospitalisation and/or assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopaenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Participants should be asked to record the following:
  - All level 2 and 3 hypoglycaemic events.
  - All symptomatic hypoglycaemic events for 2 weeks before baseline (i.e. Visit 3) and 2 weeks before week 16 (i.e. Visit 7).

Questionnaires WPG

- The latest approved version of the questionnaires must be used.
- Ensure the patient identification number, the correct visit number and date of visit are entered on each page.
- The questionnaires are intended for self-completion on the day of visit.
- If the respondent is unable to complete the questionnaire by themselves, it may help for the researcher to read aloud the questionnaire. It is acceptable for a third party to record the respondent's replies but care should be taken to avoid prompting.
- If the respondent finds statements too limiting the researcher should remind the participant of the questionnaire instruction (e.g. "Questions refer to your heart failure and how it may affect your life") and reinforce that there are no right or wrong answers (i.e. do not give any prompts and make it clear that it is the respondent's own evaluation that is required).
- The researcher should check the questionnaire for completeness and go through any missing questions or ambiguous answers (e.g. 2 answers ticked instead of one) with the participant.

6-minute walk test WPG (Part 1 of 3)

This test assesses the distance (in metres) an individual can walk in 6 minutes.

Equipment

- Chair, stopwatch, pre-measured marks along corridor, clipboard with paper and pen.

Procedure

- Perform test along a 20 meters flat, straight course with a hard surface and little pedestrian traffic. Providing a chair may be useful in case participant needs to rest during or after the test.
- Participants should wear comfortable clothing and appropriate shoes for walking. If participant has walking aids these should be used and documented.
- Participants should be provided with the test standardised instructions (see part 2 of 3) before the test and encouraged during the tests using standardised phrases (see part 3 of 3) .
- The participants should be positioned at the start of the marked corridor and the timer started as they start to walk.
- The participant should walk back and forth along the marked walkway at their own pace.
- The total distance walked should be recorded, rounding to the nearest metre. If the patient stopped during the test, the researcher should record total number of stops.

6-minute walk test WPG (Part 2 of 3)

Standardised instructions should be provided to the participant as below:

1. “The aim of this test is to walk as far as possible for 6 minutes. You will walk along this hallway between the markers, as many times as you can in 6 minutes.”

2. “I will let you know as each minute goes past, and then at 6 minutes I will ask you to stop where you are.”

3. “6 minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary, but please resume walking as soon as you are able.

4. “Remember that the objective is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog.

5. “Do you have any questions?”

6-minute walk test WPG (Part 3 of 3)

Standardised encouragement should be provided every minute as described below:

1 min – “You are doing well. You have 5 minutes to go.”

2 min – “Keep up the good work. You have 4 minutes to go.”

3 min – “You are doing well. You are halfway.”

4 min – “Keep up the good work. You have only 2 minutes left.”

5 min – “You are doing well. You have only 1 minute to go.”

6 min – “Please stop where you are.”

Every 30s if the patient stops during the test: “Please resume walking whenever you feel able.”

Urine Pregnancy test

- Carried out for women of childbearing potential.

Urine samples

- Collected, processed and stored as per laboratory manual.
- Albumin, creatinine and sodium will be analysed by the local NHS laboratory.
- Additional optional research urine sample to be collected for future research, if consented.

Blood samples

- Collected, processed and stored as per laboratory manual.
- Full blood count, urea and electrolytes, liver function tests, glucose and HbA1c will be analysed by the local NHS laboratory.
- Screening NT-proBNP (or BNP depending on local laboratory availability) will be performed in the local NHS laboratory, if a result is not available within 12 months of screening.
- Research blood samples for NT-proBNP (at baseline and week 16) and C-peptide (at baseline) will be processed, stored frozen and shipped to Dundee for analysis at the end of trial.
- Additional optional research blood samples to be collected for future research/genetic analysis, if consented.