FULL/LONG TITLE OF THE TRIAL

A phase 2 double-blind randomised controlled trial studying the effect of sotagliflozin 200mg once daily versus placebo in individuals with heart failure and type 1 diabetes on quality of life measured using the Kansas City Cardiomyopathy Questionnaire.

SHORT TRIAL TITLE / ACRONYM

SOtagliflozin in **P**atients with **H**eart fa**i**lure **S**ymptoms and **T**ype 1 Diabetes - **SOPHIST**

PROTOCOL VERSION NUMBER AND DATE

SOPHIST Protocol V6 13-11-2025.docx

RESEARCH REFERENCE NUMBERS

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SPONSOR'S Number:	01-50-23
FUNDERS Number:	3-SRA-2023-1376-M-B

This protocol has regard for the HRA guidance and order of content V1.2 March 2016

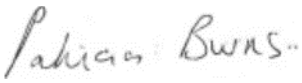
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator (CI) agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) standard operating procedures, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor

Signature: 

Date: 19.12.2025

Name: Patricia Burns

Position: Senior Research Governance Manager

Chief Investigator

Signature: 

Date: 13/11/2025

Name: Dr Ify Mordi

Statistician

Signature: 

Date:13/11/2025

Name: Dr Adrian Hapca

Position: TCTU Clinical Trial Statistician

KEY TRIAL CONTACTS

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Trial Coordinator	Margaret Band, Senior Trial Manager, Tayside Clinical Trials Unit (TCTU), Tayside Medical Science Centre (TASC), Residency Block, Level 3, Ninewells Hospital, Dundee, DD1 9SY 01382383097 m.band@dundee.ac.uk
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LIST of CONTENTS

I. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
bPIS	brief Participant Information Sheet
CGM	Continuous Glucose Monitor
CI	Chief Investigator
CMR	Cardiac Magnetic Resonance Imaging
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
DTSQ	Diabetes Treatment Satisfaction Questionnaire
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
ECV	Extracellular Volume
FBC	Full blood count
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c
HF	Heart Failure
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PI	Principal Investigator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SHARE	Scottish Health Research Register & Biobank
SGLTi	Sodium-glucose co-transporter inhibitors
SGLT2	Sodium-glucose Cotransporter-2
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TASC	Tayside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group
TRuST	Tayside Randomisation System
TSC	Trial Steering Committee
UoD	University of Dundee
WOCBP	Women of Childbearing Potential
QoL	Quality of Life

II. TRIAL SUMMARY

Trial Title	A phase 2 double-blind randomised controlled trial studying the effect of sotagliflozin 200mg once daily versus placebo in individuals with heart failure and type 1 diabetes on quality of life measured using the Kansas City Cardiomyopathy Questionnaire.	
Short Title	**SO**tagliflozin in **P**atients with **H**eart fa**i**lure **S**ymptoms and **T**ype 1 Diabetes - **SOPHIST**	
Clinical Phase	II	
Trial Design	Multi-centre, parallel-group, double-blind randomised controlled trial	
Trial Participants	Adults with type 1 diabetes and symptomatic heart failure.	
Planned Sample Size	320	
Treatment duration	16 weeks	
Follow-up duration	4 weeks	
Planned Trial Period	20 weeks	
	Objectives	Outcome Measures
Primary	To investigate the effect of sotagliflozin on quality of life (QoL)	Kansas City Cardiomyopathy Questionnaire (KCCQ)
Secondary	To investigate the effect of sotagliflozin on walking distance	6-minute walk test
	To investigate the effect of sotagliflozin N-terminal pro B-type natriuretic peptide (NT-proBNP)	NT-proBNP
	To provide information on safety and tolerability of sotagliflozin	Severe hypoglycaemia, diabetic ketoacidosis (DKA)
Investigational Medicinal Product (IMP)	Sotagliflozin or matched placebo.	
Formulation, Dose, Route of Administration	200mg oral tablets, once daily	

III. SUB-STUDY SUMMARY

Sub-study Title	SOPHIST sub-study examining the effect of Sotagliflozin on myocardial blood flow in participants with Type 1 Diabetes and Heart Failure symptoms	
Short Title	SOPHIST Cardiac Magnetic Resonance (CMR) Sub-study	
Sub-study Design	Multi-centre, parallel group, pre-post mechanistic sub-study	
Sub-study Participants	A subset of participants from the SOPHIST trial, that meet additional sub-study eligibility criteria, will be invited to participate.	
Planned Sample Size	44	
Planned Sub-study Period	16 weeks	
	Objectives	Outcome Measures
Primary	To investigate the effect of sotagliflozin on myocardial blood flow	Global stress myocardial blood flow (mL/g/min) (measured using CMR)
Secondary	To investigate the effect of sotagliflozin on myocardial blood flow and structure	Global myocardial perfusion reserve index (units)
		Global myocardial rest blood flow (mL/g/min)
		Extracellular volume fraction (%)

IV. FUNDING AND SUPPORT IN KIND

Funder(s)	**Financial and non-financial support given**
JDRF Ltd	Financial support
Lexicon Pharmaceuticals	Provision of IMP and matched placebo

CRM sub-study

Funder(s)	**Financial and non-financial support given**
British Heart Foundation (FS/ICRF/24/26101)	Financial support

V. ROLE OF TRIAL SPONSOR AND FUNDER

The roles and responsibilities of the Sponsor and Funder will be detailed in the Clinical Research Agreement.

VI. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The trial will be coordinated by a Trial Management Group (TMG), consisting of the grant holders, including the CI, collaborators, statistician, research assistant, trial manager and research nurse where appropriate. Details of membership of the TMG will be held in the Trial Master File (TMF). The TMG will meet regularly to ensure all practical details of the trial are progressing and working well and everyone within the trial understands them. Minutes of the TMG meetings will be maintained in the TMF.

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the TSC are detailed in the TMF. Minutes of the TSC will be maintained in the TMF.

A Data Monitoring Committee (DMC) will be established to oversee the safety of trial participants. The DMC will be independent of the Sponsor and will be composed of three members, a physician with experience in diabetes, a physician with experience in cardiology and a Statistician with experience in clinical trial statistical analysis, any competing interests will be declared. The DMC will be unblinded to allocation. The terms of reference of the DMC are detailed in the DMC Charter and held in the TMF. Minutes of the DMC will be held by the DMC and filed in the TMF post data lock.

An independent blinded committee for adjudication of DKA and severe hypoglycaemic events will also be established. This committee will review data related to DKA and severe hypoglycaemic events reported during the course of the trial and will confirm or reject the final diagnosis. This committee will provide further data to the DMC on these specific events.

The CI will be responsible for the conduct of the trial. Site Principal investigators (PI) will oversee the trial and will be accountable to the CI. A trial-specific Delegation Log will be prepared for the trial site, detailing the duties of each member of staff working on the trial.

The CMR sub-study will be overseen by the main trial committees and TMG.

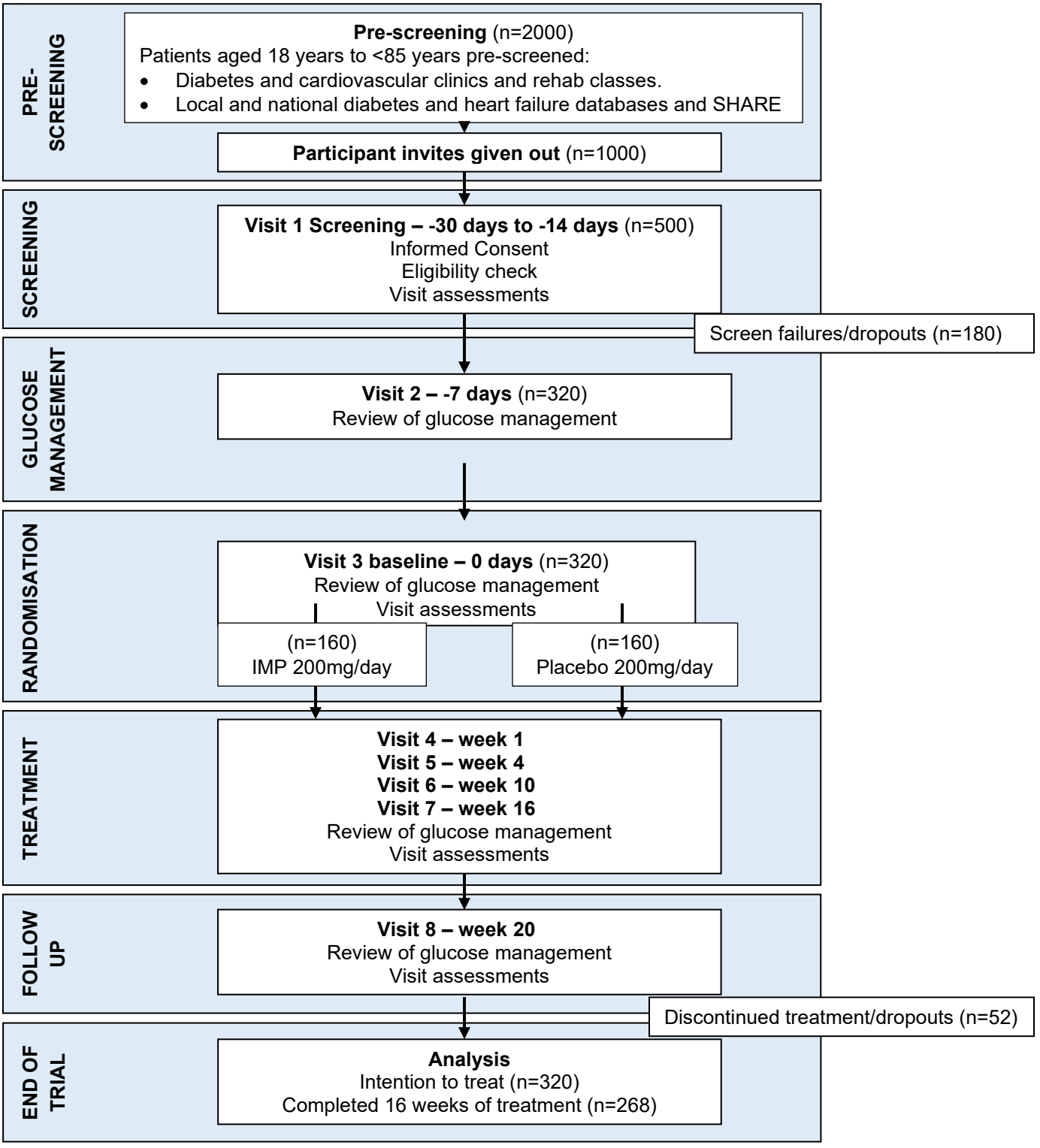
VII. PROTOCOL CONTRIBUTORS

Chief Investigator: Dr Ify Mordi, Sample size calculation, review, final approval
TCTU Senior Trial Manager: Margaret Band, initial draft, review
Collaborators: Prof Chim Lang, Prof Rory McCrimmon, Prof Ewan Pearson, review
TCTU Statistician: Dr Adrian Hapca, review
Clinical Trial Pharmacist: Shona Carson, review
TCTU Database Manager: Marcus Achison, review

VIII. KEY WORDS:

Type 1 diabetes; heart failure; Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors, sotagliflozin

IX. TRIAL FLOW CHART



1. BACKGROUND

Intensive insulin therapy designed to near-normalize glucose levels in people with type 1 diabetes significantly reduces an individual's risk of long-term micro- and macrovascular complications[1]. Unfortunately, glycaemic targets are not achieved by the majority of people with type 1 diabetes[2] and as such overall life expectancy remains reduced compared to those without type 1 diabetes[3]. Cardiovascular disease remains a major cause of morbidity and mortality in type 1 diabetes[4]. There is growing recognition that heart failure (HF) is an increasing problem in type 1 diabetes. Diabetes itself is an independent risk factor for HF[5,6], causing structural and functional cardiac changes that predispose to HF (known as diabetic cardiomyopathy)[7]. HF is the end result of many cardiovascular diseases such as hypertension and myocardial infarction, and improved treatments for these conditions and changing demographic trends mean that many more people are surviving longer and developing HF[8].

HF has a substantial healthcare burden. In the US and Europe, the prevalence of HF in the general population is around 1-2% - around 6 million adults in the US are estimated to be living with HF currently[9]. In 2014 in the US there were ~1.1 million emergency department visits,

980 000 hospitalizations, and 84 000 deaths with HF as the primary cause[10], with an estimated cost of ~$11.3 billion (~$11,500/per patient for each hospitalisation). Despite advances in management of HF over the past 30 years, the incidence of mortality and HF hospitalisation in recent HF clinical trials remained high at ~20-30% over 2 years[11-13].

The burden of HF in type 1 diabetes is less well characterised compared to HF in those with type 2 diabetes (and individuals without diabetes), however the data still indicate the substantial nature of this growing problem[14]. One of the largest epidemiological studies was a Scottish national data study of 3.25 million individuals >30 years old, where the crude incidence of HF hospitalisation was over twice that of the population without diabetes[15]. While the crude incidence was less than in type 2 diabetes, type 1 diabetes patients were on average 20 years younger. Despite their younger age, 30-day mortality following HF hospitalisation was higher in individuals with type 1 diabetes after adjustment for age, sex and socioeconomic status, indicating that outcomes are worse in HF patients with type 1 diabetes compared to those with either type 2 diabetes or without diabetes. Data from Scandinavia supports this finding and suggests that the risk of both incident HF and cardiovascular mortality was higher for individuals with type 1 diabetes compared to type 2 diabetes after adjustment for age[16]. The overall prevalence of HF in this study at baseline was 3.1% - extrapolated to the US this would equate to 57,000 of the 1.9 million individuals with type 1 diabetes. A recent meta-analysis of all available data suggested that the incidence of HF was 3.1 times higher in individuals with type 1 diabetes compared to controls (typically the general population)[17]. Assuming a 5% incidence of HF hospitalisation/year, HF hospitalizations cost the US healthcare system ~$29 million per year. In summary, these data suggest that not only is HF a significant problem in individuals with type 1 diabetes, but there is evidence of an outcome disparity compared to individuals with type 2 diabetes or those without diabetes.

Although there are some differences (e.g. presentation at a younger age), the pathophysiology of HF in type 1 diabetes is similar to type 2 diabetes. Risk factors are similar (e.g. glycaemic control, coronary artery disease and hypertension), leading to inflammation, endothelial dysfunction, fibrosis, and subsequent diastolic and systolic dysfunction[14]. Given the pathophysiological

similarities, there is little to suggest that HF therapies that have shown benefit in individuals with type 2 diabetes (or individuals without diabetes) would not also be efficacious in type 1 diabetes. In all current HF guidelines mainstay HF treatments (renin-angiotensin system blockers, beta-blockers, and mineralocorticoid receptor antagonists) are recommended for all patients with HF regardless of diabetes status.

Sodium-glucose co-transporter inhibitors (SGLTi) were initially developed as oral add-on treatments for glycaemic control in type 2 diabetes. A consistent finding in large cardiovascular outcome trials was a significant ~30% risk reduction in hospitalisation for HF, as well as overall reductions in cardiovascular mortality[18]. Subsequently, SGLTi in addition to guideline-directed HF therapy have been studied in HF patients either with type 2 diabetes or without diabetes and have again shown a consistent benefit compared to placebo, with significant reductions in mortality and HF hospitalisation irrespective of cardiac function left ventricular ejection fraction (LVEF) at baseline without any concerning safety signals (Table 1)[13,19]. SGLTi also improve HF-related QoL and renal outcomes[20]. This has led to the inclusion of SGLTi in the most recent HF treatment guidelines as a cornerstone of therapy in addition to established pharmacological agents (e.g., renin-angiotensin system inhibitors, beta-blockers and mineralocorticoid receptor antagonists). However, there is one key issue - individuals with type 1 diabetes have been excluded from these HF trials, in part due to concerns around safety. At present there is no evidence to support the use of these life-saving therapies in this population that already has worse outcomes than other groups with HF.

Table 1. Summary of SGLTi Cardiovascular Outcome Trials in HF Patients

Trial	**Intervention**	**Number of Patients**	**Diabetes Status**	**LVEF[a]**	**Relative Reduction in Primary endpoint with SGLTi v placebo**	**Relative Reduction in HF hospitalisation with SGLTi vs. placebo**	**Improvement in KCCQ[b] score vs. placebo (at timepoint)**
SOLOIST-WHF[22]	Sotagliflozin	1222	Type 2 diabetes	Any	33%	36%	4.1 (1.3-7.0) (4 months)
DAPA-HF[11]	Dapagliflozin	4744	Type 2 diabetes or no diabetes	≤40%	26%	30%	1.80 (4 months)
DELIVER[21]	Dapagliflozin	6263	Type 2 diabetes or no diabetes	>40%	18%	23%	1.9 (1.1-2.7) (4 months)
EMPEROR-Reduced[12]	Empagliflozin	3730	Type 2 diabetes or no diabetes	≤40%	25%	31%	1.94 (0.96-2.93) (3 months)
EMPEROR-Preserved[13]	Empagliflozin	5988	Type 2 diabetes or no diabetes	>40%	21%	27%	1.03 (0.32-1.74) (3 months)

[a]LVEF – left ventricular ejection fraction. Primary endpoints in clinical trials were typically time to cardiovascular death and/or first HF hospitalisation.
[b]KCCQ – Kansas City Cardiomyopathy Questionnaire, a validated measure of QoL in HF patients commonly used as a surrogate efficacy outcome.

In adult type 1 diabetes, Phase III trials with dapagliflozin[23,24], empagliflozin[25] and sotagliflozin[26,27] have been completed, collectively showing modest benefits of SGLT inhibition in terms of Haemoglobin A1c (HbA1c) reduction, increased time in range, reduced body weight and total insulin dose. However, SGLTi use in type 1 diabetes was also associated with an increased risk of DKA[28], which has limited their more widespread use in type 1 diabetes.

Sotagliflozin is a dual SGLT1 and 2 inhibitor that is currently approved in the United Kingdom for use in individuals with type 1 diabetes with a body mass index (BMI) of ≥27kg/m2 and taking insulin doses of at least 0.5 units/kg of body weight in patients with inadequate glycaemic control[26]. As with selective SGLT2i, sotagliflozin also improves HF-related outcomes. The key evidence for this comes from two clinical trials. In the Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease (SCORED) trial[22] including 10,584 patients with type 2 diabetes, chronic kidney disease and cardiovascular risk factors, sotagliflozin caused a 26% relative risk reduction in the primary endpoint of cardiovascular death, HF hospitalisation or urgent HF visit compared to placebo. There was also a 33% relative risk reduction in HF hospitalisation or urgent HF visits, figures consistent with other SGLT2i trials.

The second key trial was the Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure (SOLOIST-WHF) trial[22]. In this trial 1,222 patients with type 2 diabetes and a recent HF hospitalisation were randomised to sotagliflozin 200mg once daily (with uptitration to 400mg once daily) or placebo. Patients were included regardless of LVEF at baseline. The median follow-up duration was 9 months.

Sotagliflozin caused a 33% relative risk reduction in the primary outcome of cardiovascular death, HF hospitalisation or urgent HF visit, with a 36% reduction in HF hospitalisation or urgent HF visits that met statistical significance. Sotagliflozin also significantly improved QoL at 4 months measured using the KCCQ. Rates of SAEs leading to study drug withdrawal were similar in both sotagliflozin and placebo groups, though severe hypoglycaemia was more common with sotagliflozin than placebo (9 individuals vs. 2). There was no significant increase in incidence of DKA with sotagliflozin compared to placebo (2 vs. 4). Taken together, these two trials confirm the benefit of sotagliflozin on HF related outcomes, consistent with selective SGLT2i. Again, individuals with type 1 diabetes were excluded from both of these trials.

In summary, there is significant HF related morbidity and mortality in type 1 diabetes, and outcomes are worse than in HF patients with type 2 diabetes or without diabetes. Oral sotagliflozin 200mg daily is licensed for improving glycaemic control in type 1 diabetes in the UK. Although sotagliflozin improves HF related outcomes and QoL in patients with type 2 diabetes and patients with HF who do not have diabetes, studies are needed to determine whether these benefits might extend to patients with type 1 diabetes and heart failure.

Cardiac Magnetic Resonance Imaging (CMR) sub-study background

SGLT inhibitors such as sotagliflozin improve outcomes for HF patients, however, the underlying mechanisms remain unclear. One potential factor is microvascular disease, which is common in individuals with type 1 diabetes and can affect the heart (i.e. cardiac microvascular disease). Cardiac microvascular dysfunction impairs myocardial perfusion, a common impairment in patients with type 1 diabetes and HF. Therefore, it is important to investigate whether SGLT inhibitors improve myocardial perfusion, potentially contributing to their beneficial effects in this

vulnerable population. The CMR sub-study will investigate the impact of sotagliflozin on myocardial blood flow perfusion and whether this might contribute to its beneficial effects in HF.

2. RATIONALE

As outlined above, HF is a significant problem in type 1 diabetes, with an estimated prevalence of 3-5%. Outcomes for individuals with type 1 diabetes and HF are worse than in those with type 2 diabetes or without diabetes, with increased mortality and hospitalisation rates. Critically, patients with type 1 diabetes have been excluded from pivotal trials of the latest advance in HF treatment (SGLT2i), potentially exacerbating these outcome disparities further.

The proposed trial will be the first to provide data on the efficacy and safety of sotagliflozin, in patients with type 1 diabetes and HF (regardless of LVEF). If a beneficial signal is found, this would provide strong support for extending the use of sotagliflozin in this group of patients with type 1 diabetes and adoption into clinical guidelines. A multi-centre, double-blind, randomised controlled trial to provide the strongest level of evidence for previous findings of the researchers will be conducted. Importantly, by choosing QoL measured using the KCCQ as the primary endpoint, an outcome that not only correlates strongly with mortality and hospitalisation but is also accepted by the US Food and Drug Administration as a valid endpoint for regulatory approval has been selected. The KCCQ is a 23-item self-administered questionnaire that measures the patient's perception of their health status, including HF symptoms, impact on physical and social function, and how their HF impacts their QOL within the preceding 2 weeks[29]. Improvements in KCCQ score map very well to reductions in mortality and hospitalisation and SGLT2i have consistently improved KCCQ scores (Table 2). A 5-point increase in KCCQ score is traditionally considered clinically meaningful and is associated with a 7% reduction in mortality and HF hospitalisation[30]. Given the prohibitive size of trial that would be required to demonstrate an improvement in mortality or HF hospitalizations with sotagliflozin in type 1 diabetes, the KCCQ represents an ideal endpoint for the trial. The proposed trial has the potential to be a high-impact, practice-changing trial.

Table 2. Summary of SGLT2i vs. placebo randomised trials in HF patients with QoL measured by KCCQ as the primary endpoint.

Trial	Intervention	Number of Participants	Diabetes Status	LVEF	KCCQ improvement at 3 months (SD)
DEFINE-HF[31]	Dapagliflozin	263	Type 2 diabetes or no diabetes	<40%	4.7
PRESERVED-HF[32]	Dapagliflozin	324	Type 2 diabetes or no diabetes	>40%	5.8 (2.0-9.6)
EMPULSE[33]	Empagliflozin	530	Type 2 diabetes or no diabetes	Any	4.45 (0.32-8.59)
CHIEF-HF[34]	Canagliflozin	476	Type 2 diabetes or no diabetes	Any	3.7 (0.5-7.0)

CMR sub-study rationale

The mechanism of benefit of SGLT inhibitors in people with heart failure is unknown. While some studies[42-44] suggest SGLT inhibitors might improve myocardial perfusion in type 2 diabetes without HF, these findings have not been consistently replicated[45,46]. Importantly, these studies did not include participants with HF or type 1 diabetes, populations where cardiac microvascular disease is likely more severe (e.g. most participants in these published clinical studies had normal myocardial perfusion). Therefore, it is feasible that changes in microvascular function could be important in patients with type 1 diabetes and HF and potentially relevant to the benefits of SGLT inhibitors in this cohort. Given the limitations of previous research, the SOPHIST trial provides a valuable opportunity to investigate this relationship in a cohort of patients with type 1 diabetes and HF.

The primary rationale for this CMR sub-study is to determine whether 16 weeks of sotagliflozin treatment improves myocardial blood flow compared to placebo. Participants will undergo CMR scans at baseline and 16 weeks. The administration of intravenous gadolinium contrast while the heart is at rest and under stress (induced by intravenous adenosine) allows for an assessment of myocardial blood flow (as a measure of cardiac microvascular function). Participation requires enrolment in the main SOPHIST trial, written informed consent for the sub-study, and a reasonable expectation of compliance with both scans from the participant and research staff.

2.1. Assessment and Management of Risk

This trial is categorised as:

- Type B = Somewhat higher than the risk of standard medical care

To date, the following are the risks identified for sotagliflozin:
Diabetic Ketoacidosis (DKA) (3%): SGLT2i therapy in type 1 diabetes is associated with an increased risk (~3%) of DKA[35]. If severe, this can lead to hospitalization (and if untreated, death). The incidence of positively-adjudicated DKA in the InTandem programme[36] was 2.7% (16 events) in those taking sotagliflozin 200mg compared to 0.5% (1 event) in the individuals on placebo. Nearly all DKA events led to hospitalization and were thus classified as serious adverse events (SAE). However, there were no deaths or persistent sequelae from any events. Importantly, these data were obtained before the use of a structured education programme, and without the labelling now provided with sotagliflozin. Additionally, DKA was more common in those with BMI <27kg/m2 and in those on lower insulin doses.

Participants will be managed as described in section 7.8.

Hypoglycaemia (3%): Incidence of severe hypoglycaemia was 3% in individuals taking sotagliflozin vs. 2.4% in the placebo group in the inTandem3 trial[26]. This was defined as a hypoglycaemic event requiring assistance from another person or resulted in a loss of consciousness or seizure. Pooled data from the inTandem 1 and 2 trials demonstrated similar incidence of severe hypoglycaemia at 52 weeks (2-3%) with sotagliflozin in individuals with type 1 diabetes that was lower than the incidence in the placebo group[37]. Risk of seizures or cardiac arrhythmias due to hypoglycaemia is typically <0.1%.

Genital/Urinary Tract Infections (5%): Due to glycosuria there is an increased likelihood of genital or urinary infections. These are more common in patients with a history of urinary infections. The

majority of these infections are fungal in nature (vaginal or penile candidiasis) and treated with topical agents.

Fournier's Gangrene: SGLT2 inhibitors have been associated with a very rare but serious risk of necrotising fasciitis of the perineum (Fournier’s gangrene). While precise statistics on the increased risk in type 1 diabetes are limited, type 1 diabetes is considered a risk factor due to potential immune dysfunction and increased susceptibility to infection. Reports of Fournier's gangrene, a very rare but serious and life-threatening necrotising infection requiring urgent surgical intervention, have been identified in post marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors. Cases have been reported in both men and women. Serious outcomes have included hospitalisation, multiple surgeries, and death. It is important to note that the overall risk remains very rare. Symptoms may include pain or tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise.

Volume Depletion (2%): This usually occurs in the context of an intercurrent illness (for example diarrhoea or vomiting).

Blood creatinine increase/glomerular filtration decrease and renal-related events (1-2%): Sotagliflozin was associated with decreases in mean estimated glomerular filtration rate (eGFR), at week 4 (-4.0% and -4.3% for sotagliflozin 200 mg and 400 mg) versus placebo (-1.3%) that were generally reversible during continuous treatment. Mean increases in serum creatinine from baseline to week 4 were 4.0%, 4.3% and 1.4% for sotagliflozin 200mg, sotagliflozin 400 mg and placebo, respectively. At week 24 and 52 the change from baseline in creatinine was equal to or less than 0.02 mg/dl for both sotagliflozin 200 and sotagliflozin 400mg. The incidence of renal-related events was low and similar across the groups (1.5%, 1.5% and 1.3% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo). It should be noted that this pattern of renal function change (i.e. an initial decline in renal function followed by a stabilisation and improvement compared to placebo over time) is consistent with other SGLTi that demonstrate long-term renoprotective effects.

To date, the risks identified for CMR are:

Gadolinium contrast - small risk of Nephrogenic systemic fibrosis (NSF) and rare hypersensitivity reactions.

Adenosine – common short-lived symptoms (maximum couple of minutes while infusion running) of chest tightness, shortness of breath or mild nausea. Rarely adenosine may induce arrhythmias, hypotension or bronchospasm, particularly in susceptive individuals.

Implantable devices and metallic foreign bodies – strong magnetic field can move or heat metal objects, which can cause injury or device malfunction.

All risks are minimised through established safety protocols and participant screening.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The primary objective of the SOPHIST trial is to investigate the effect of 16-week treatment with sotagliflozin in addition to standard of care on QoL compared to placebo in participants with type 1 diabetes and HF symptoms.

3.1. CMR sub-study objectives

The primary objective of the CMR sub-study is to investigate the effect of 16 weeks treatment with sotagliflozin in addition to standard of care on myocardial blood flow compared to placebo in individuals with HF and type 1 diabetes.

3.2. Table of endpoints/outcomes

Primary Objective		
Objectives	**Outcome Measures**	**Timepoint(s)**
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on quality of life	Change from baseline in KCCQ clinical summary score	Weeks 0 and 16

Secondary Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on QoL	Change from baseline in KCCQ clinical summary score	Weeks 0 and 4
	Change from baseline in KCCQ overall summary score	Weeks 0, 4 and 16
	Proportion of participants with a ≥5, ≥10 and ≥15 point increase in KCCQ clinical and overall summary scores	Weeks 0 and 16
	Change from baseline in Diabetes Treatment Satisfaction Questionnaire (DTSQs and DTSQc)	Weeks 0 and 16
	Change from baseline in EQ-5D-5L score	Weeks 0 and 16
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on walking distance	Change from baseline in distance covered during 6-minute walk test	Weeks 0 and 16
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on NT-proBNP	Change from baseline in NT-proBNP	Weeks 0 and 16
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on glycaemic control	Change from screening in HbA1c	Screening and week 16

To provide information on safety and tolerability of sotagliflozin 200mg once daily in addition to standard of care compared to placebo	Proportion of participants with level 2 or level 3 hypoglycaemia	Week 0 to weeks 16 and 20
	Proportion of participants with DKA	Week 0 to weeks 16 and 20
	Proportion of participants requiring hospitalisation due to HF	

Exploratory Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on HF symptoms, signs and clinical outcomes	Change from screening in New York Heart Association (NYHA) class	Screening, weeks 16 and 20
	Change from baseline in daily loop diuretic dose	Weeks 0 and 16
	Change from baseline in systolic and diastolic blood pressure.	Weeks 0 and 16
	Number of hospitalizations and deaths (first and total number) due to heart failure	Week 0 to weeks 16 and 20
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on renal parameters	Change from baseline in eGFR, serum creatinine, urine albumin to creatinine ratio	Weeks 0 and 16
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on diabetes-related parameters	Change from baseline in total, basal and bolus insulin doses.	Weeks 0, 4 and 16
	Change from baseline in body weight.	Weeks 0 and 16
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on Continuous Glucose Monitor (CGM) metrics recommended by the international consensus on the use of CGM[38]	Mean blood glucose level over preceding 14 days	Weeks 0, 4 and 16
	Blood glucose percentage time in range (3.9-10.0 mmol/L) over preceding 14 days	Weeks 0, 4 and 16
	Blood glucose percentage time below range (3.0-3.8 mmol/L and <3.0 mmol/L) over preceding 14 days	Weeks 0, 4 and 16
	Blood glucose percentage time above range (10.1-13.9mmol/L and >13.9 mmol/L) over preceding 14 days	Weeks 0, 4 and 16
	Glycaemic variability index	Weeks 0, 4 and 16

To investigate if trial outcomes are associated with baseline c-peptide levels	C-peptide level at baseline	Week 0
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on ketone levels	Proportion of participants with non-acidotic ketosis (blood ketones >1.5mmol/L, blood pH of ≥7.3, bicarbonate ≥18mmol/l)	Weeks 0 and 16

3.3. Table of endpoints/outcomes (CMR sub-study)

Primary Objective		
Objectives	**Outcome Measures**	**Timepoint(s)**
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on myocardial blood flow compared to placebo.	Change in global stress myocardial blood flow (mL/g/min) (measured using CMR)	Weeks 0 and 16
Secondary Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on myocardial blood flow and cardiac structure compared to placebo.	Change in global myocardial perfusion reserve index (units)	Weeks 0 and 16
	Change in global myocardial rest blood flow (mL/g/min)	Weeks 0 and 16
	Change in extracellular volume fraction (%)	Weeks 0 and 16
Exploratory Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
To investigate the effect of sotagliflozin 200mg once daily in addition to standard of care on cardiac function compared to placebo.	Change in left ventricular ejection fraction (%)	Weeks 0 and 16
	Change in left atrial volume (mL/m^2)	Weeks 0 and 16
To evaluate whether changes in myocardial blood flow mediate or influence changes in main trial outcomes (as defined in Section 3.2).	Analyses will assess changes in myocardial blood flow and associations with changes in all main trial outcomes (Section 3.2).	Weeks 0 and 16

4. TRIAL DESIGN

A multi-centre, parallel-group, double-blind randomised controlled trial of sotagliflozin 200mg versus placebo, once daily in addition to standard of care in 320 adults with type 1 diabetes and HF in the UK. After receiving informed consent participants will be randomised in a 1:1 allocation to 16 weeks of oral sotagliflozin 200mg or matched placebo, once daily in addition to their standard care. Both the participants and investigators will be blinded to treatment allocation.

4.1. CMR sub-study design

A subset of participants (n=44) enrolled in the main SOPHIST trial will be invited to participate in a CMR sub-study at selected sites (including Dundee - the lead site for main trial and sub-study). Participants in the CMR sub-study will undergo CMR scans at baseline and after 16 weeks of treatment in addition to the standard trial assessments. CMR is intended to reflect the pre-treatment state and the effects of treatment in the preceding weeks.

5. TRIAL SETTING

Participants will be identified and recruited through NHS secondary care services. Potential participants may also be identified from the databases of the NHS Research Scotland Diabetes Network, Diabetes Research Register and the Scottish Health Research Register & Biobank (SHARE), Clinical Research Networks and local research registries. Where sites wish, primary care or patient identification centres may also be used.

The research activities will take place in approximately 12-15 secondary care settings within NHS trusts across the UK with the potential to include more sites depending on recruitment needs.

6. PARTICIPANT ELIGIBILITY CRITERIA

Patients are potentially eligible for SOPHIST if they have either a previous confirmed diagnosis of heart failure or undiagnosed heart failure. In recognition of this, we have included criteria to help identify those at higher risk of having undiagnosed heart failure who could be invited for screening:

6.1. For Screening visit

6.1.1. Eligibility

1. Age 18 years to <85 years.
2. Type 1 diabetes.
3. Meets the NTproBNP or echocardiographic randomisation inclusion criteria below
   OR
   Any of the following:
   - Type 1 diabetes for >25 years **and** >40 years old

   or
   - History of any cardiac disease, for example but not limited to:
     - Hypertension, cardiac arrhythmia, myocardial infarction, angina, hyperlipidaemia

   or

- History of any vascular disease, for example but not limited to:
    - Stroke, transient ischaemic attack, peripheral vascular disease, diabetic foot disease, vascular ulcer

or

- History of diabetic retinopathy

or

- History of renal disease, for example but not limited to:
    - Microalbuminuria (urine albumin/creatinine ratio ≥ 3 mg/mmol)

or

- Taking medications for any of the above, for example but not limited to:
    - Angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), betablockers, calcium channel blockers, loop diuretics, thiazides, mineralocorticoid receptor antagonists, antiplatelets, anticoagulants

6.2. For randomisation

6.2.1. Inclusion criteria

1. Age 18 years to <85 years.
2. Type 1 diabetes.
3. Insulin dose ≥0.5 units/kg body weight at screening **or** BMI ≥25kg/m^2 at screening
4. Using continuous glucose monitor at screening or willing to use one for the duration of the trial.
5. Diagnosis of heart failure (HF) or high-risk for HF, defined as any of the following:
   NT-proBNP ≥250ng/L for those in atrial fibrillation/flutter, ≥125 ng/L for those in all other rhythms

or

Previous HF hospitalisation where HF was documented as the primary cause of hospitalisation and there was a requirement for loop diuretics

or

Impaired left ventricular (LV) function (i.e. LVEF <50% by any imaging modality) at any time

or

Preserved LV systolic function (LVEF ≥50%) with left atrial enlargement (2-dimensional measurement of left atrial width ≥3.8cm or left atrial length ≥5.0 cm or left atrial area ≥20cm^2 or left atrial volume index >29 ml/m^2) within the last 24 months.

or

Preserved LV systolic function (LVEF ≥50%) with left ventricular hypertrophy (2-dimensional measurement of end-diastolic interventricular septal diameter ≥1.2cm or end-diastolic left ventricular posterior wall diameter ≥1.2cm) within the last 24 months.

or

Preserved LV systolic function (LVEF ≥50%) with diastolic dysfunction (septal e' <7cm/sec or lateral e' <10cm/sec or average E/e' ≥15) within the last 24 months.

6. New York Heart Association Class II-IV at screening.
7. Kansas City Cardiomyopathy clinical summary score <85 at screening.

6.3. Exclusion criteria

1. Cardiac surgery (coronary artery bypass graft or valve replacement), type 1 myocardial infarction, implantation of cardiac device (including biventricular pacemaker) or cardiac mechanical support implantation within 1 month of screening, or between screening and randomisation, or planned during the trial.
2. End-stage heart failure requiring left ventricular assist devices, intra-aortic balloon pump, or any type of mechanical support at the time of randomisation.
3. Documented primary severe valvular heart disease, amyloidosis or hypertrophic cardiomyopathy as principal cause of heart failure as judged by the local investigator.
4. Respiratory disease thought to be the primary cause of dyspnoea as assessed by the local investigator.
5. Chronic kidney disease with estimated glomerular filtration rate <25ml/min/1.73m2 at screening.
6. Moderate or severe hepatic impairment (e.g. Child-Pugh B and C) at screening as judged by the local investigator.
7. Use of sotagliflozin or any SGLT2 inhibitor within 1 month of screening or between screening and randomisation.
8. Previous hypersensitivity/intolerance to SGLT2 inhibitors.
9. Presence of malignancy with expected life expectancy <1 year at screening.
10. Severe hypoglycaemia (hospitalisation for hypoglycaemia or episode requiring external assistance to treat) within 1 month prior to screening or between screening and randomisation.
11. One episode of diabetic ketoacidosis or nonketotic hyperosmolar state within 1 month of screening or between screening and randomisation, or ≥2 diabetic ketoacidosis or nonketotic hyperosmolar state events within 6 months of screening.
12. Pregnant or lactating women.
13. Women of childbearing age or male partners of women of childbearing age and not practicing an acceptable method of birth control, see section 8.11
14. On a ketogenic diet.
15. Unwilling/unable to share glucose and ketone monitoring data.
16. Use of any investigational drugs within five times of the elimination half-life after the last dose or within 30 days, whichever is longer. Current enrolment in non-interventional, observational studies will be allowed.

6.4. CMR sub-study eligibility criteria

Inclusion criteria

1. Eligible to be randomised in main trial*
2. Able to comply with sub-study procedures.
3. Written informed consent.

Exclusion criteria

1. Non-CMR compatible implantable cardiac device i.e. pacemaker, implantable defibrillator.
2. Metallic foreign bodies, including suspicion of.

3. Claustrophobia or inability to remain still during imaging.
4. Contra-indication to intravenous adenosine as judged by the investigator, i.e. asthma; severe chronic obstructive lung disease; decompensated heart failure; long QT syndrome; second- or third-degree AV block and sick sinus syndrome; severe hypotension.
5. Contra-indication/allergy to gadolinium contrast media.
6. Estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2.

*Not all information regarding final eligibility for the main trial may be known at the time of the CMR imaging as some inclusion or exclusion criteria (e.g. relating to events between screening and randomisation) may not be finalised, however the investigator will use their judgement as to the likelihood of eligibility for the main trial to facilitate recruitment into the CMR sub-study.

Participants in the CMR sub-study should meet all inclusion criteria for the main trial, and all known exclusion criteria prior to CMR. If a participant becomes ineligible for the main trial after the first CMR imaging, they will be withdrawn and no further imaging completed.

7. TRIAL PROCEDURES

All trial procedures will be carried out as per Schedule of Procedures, Appendix 4.

7.1. Recruitment

Anonymised information on participants who are not randomised will be collected for CONSORT reporting and includes:

- age,
- gender,
- ethnicity,
- the reason not eligible for trial participation, or if they are eligible but declined.

7.1.1. Participant Identification

Identification of potentially eligible trial participants by the research or clinical teams may make use of any or all of the following:

- From secondary care in-patient and out-patient services. Suggested services where participants may be identified are:
    - Diabetes services
    - Cardiovascular services, including but not limited to heart failure, arrythmia, stroke and hypertension services
    - Diabetic foot services
    - Nephrology services
    - Ophthalmology services

  Clinic lists and educational class participant lists will be reviewed by the PI or delegated member of the clinical care or trial teams (under the direction of the clinical team) and medical records checked to identify suitable participants who will then either be approached and given the brief Participant Information Sheet (bPIS) when they attend clinic or class or

will be posted an invite letter and bPIS. Contact at clinic or class will be by the PI or delegated member of the clinical care team or local clinician. Postage of invitation letters and bPIS will be carried out by the PI or delegate.

- From local diabetes or HF databases where participants have given prior consent to be contacted for future research projects, e.g., the NHS Research Scotland Diabetes Network, Diabetes Research Register or similar databases with appropriate approval in other NHS Boards/Trusts as defined locally. Local PI or delegated member of the clinical care or trial teams will send out invite letters with bPIS to individuals who may be suitable to take part.
- Recruitment of participants registered via the SHARE.
- From Clinical Research Networks, these participants will be sent out an invitation letter and bPIS.
- From primary care via the Primary Care Networks and Participant Identification Centres. These participants will be sent out an invitation letter and bPIS from the GP practice. GP practices will also be asked to display trial posters and bPIS in their waiting rooms.

When first contact is via an invitation letter a bPIS will be sent which gives a general overview of the trial. Participants will be asked to contact the trial team if they are interested in the trial. When first contact is at a hospital service, they will be given a bPIS and will be asked to either return an expression of interest or to contact a member of the trial team by telephone or email; trial staff may also arrange a convenient time to call the participant. Contact details will be provided on the bPIS.

Should individuals express an interest in taking part in the trial, the PI or delegate will contact the individual and ask for permission to check their medical notes. Individuals who returned a reply slip will have provided this permission on the slip in which case further contact with them will not be required prior to accessing their medical notes. Participants will receive a full Participant Information Sheet.

Recruitment may also utilise publicity materials including posters, information leaflets and advertisements.

The local PI will be responsible for recruitment but may delegate to other named individuals within the trial team.

Sub-study

Potential participants will be identified at participating sites based on their eligibility for both the main trial and sub-study. At the initial contact, individuals that have expressed interest in taking part, will be provided with two Participant Information Sheets (PIS) – one for the main trial and one for the sub-study. In addition, the research team may also ask potential eligible participants if they are interested in taking part in the sub-study at visit 1 or visit 2 of the main trial and provide the sub-study PIS to those that express an interest and had not yet received it.

7.1.2. Screening

At the screening visit (Visit 1), the procedures, as detailed in the Schedule of Procedures, Appendix 4, will be carried out.

Assessment of eligibility will be carried out by the PI or other medically qualified delegate. Eligibility will be confirmed at Visit 3, randomisation/baseline once all blood and echo results have been reviewed.

Details of all participants consented to the trial and screened for eligibility will be recorded on the Enrolment and Randomisation Log, this will detail if a participant fails screening or goes on to be randomised.

Where an ineligible participant's medical condition or concomitant medications change sufficiently so that they are deemed potentially eligible for the trial they may be rescreened one further time. All screening procedures will be repeated, and eligibility checked.

7.1.3. Ineligible participants

Where an individual is found to be ineligible for trial or sub-study participation, they will be thanked and the reasons for the ineligibility fully explained. Participants who are ineligible for the sub-study may still take part in the main trial if eligible. Any queries or questions will be answered by an appropriate member of the trial team. If ineligibility is related to an incidental finding (IF) which is considered to be clinically significant, it will be reported to the participant's healthcare provider e.g. GP and/or consultant by the site PI, with the consent of the individual.

7.1.4. Payment

Reasonable travel expenses for any visits additional to normal care will be given to participants.

7.2. Consent

The PI retains overall responsibility for the conduct of research at their site. This includes the taking of participants' informed consent at their site. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent according to the ethically approved protocol, principles of GCP and Declaration of Helsinki.

Where a participant requests to speak with a physician from the trial team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity their previous wishes will remain legally binding, and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the person participant's legal representative or if not contactable, a professional legal representative will be asked for their consent. In all cases the PI or delegate will consult with carers and take note of any signs of objection or distress from the participant. The participant will be withdrawn if they raise objection. Where appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from the person participant's legal representative or if not contactable, a professional legal representative to allow data collection.

7.2.1. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies.

Consent from participants will be gained for:

- use of their data in future research
- use of their specimens in future research
- use of their specimens in genetic research
- contact by trial staff for further ethically approved future research.
- enrolment for sub-study

Anonymised trial data will be kept under the control of the CI for future research use within the UoD and with other research collaborators (commercial and non-commercial).

Blood and urine will be stored for future research in laboratories at the University of Dundee. Participants will be asked at consent if they are willing for blood samples to be stored for future research, including commercial research. Specimens may be used for ethically approved research held within Tayside and will be registered with NHS Tayside Biorepository. Access for future use of those specimens will be via the CI. Not allowing blood and urine samples to be used for future research will not affect their participation in the trial. An EDTA blood sample for future genetic research will be obtained and patients will give optional consent for future genetic studies.

Where a participant subsequently rescinds their consent for this data, specimens and/or future contact, all data and specimens collected for these reasons will be destroyed. Any data collected to the point of withdrawal will be retained for reasons of public interest in the area of public health (Article 9(2)(i) GDPR).

Additional consent will be obtained from participants prior to being enrolled in the sub-study. Participation in the CMR sub-study is optional and participants may consent to the sub-study at the same time as consent to the main trial.

7.3. Randomisation scheme

Participants will be allocated to receive sotagliflozin 200 mg or matching placebo. Randomisation will be stratified according to site, presence of atrial fibrillation, renal function (eGFR <60), HbA1c >69 mmol/mol and on LVEF >40% at screening.

7.3.1. Method of implementing the randomisation/allocation sequence

After successful screening completion the participant will be assessed for eligibility for randomisation. This will be documented in the participant's medical notes and electronic Case Report Form (eCRF).

Participants will be randomised by the PI or delegate to one of the two treatment arms as noted in Section 8.1.

The PI or delegate will use a centrally controlled web based GCP compliant randomisation system, Tayside Randomisation System (TRuST), run by the UK Clinical Research Collaboration registered TCTU. TRuST is provided by the Health Informatics Centre, UoD. The Health

Informatics Centre use a validated randomisation program and will securely backup both the randomisation seed and the randomisation allocation.

Access to randomise a participant will only be given after completion of appropriate training.

7.4. Blinding

The trial will be double blinded: all participants and trial staff will be blinded to allocation. The placebo will be matched to the active tablets and labelled, prior to supplying to sites, so as not to cause unblinding.

Unblinding will only occur in an emergency, for reporting of SUSARs and at the end of the trial after data lock has occurred.

Participants will not be able to request to be unblinded. Participants will be informed of the results of the trial and their treatment allocation once the trial results have been published.

7.5. Emergency Unblinding

Unblinding will only be carried out where a physician considers that it is necessary for clinical safety.

TCTU will provide each PI with a login to the interactive web-based randomisation system, TRuST, for 24-hour emergency unblinding at their site only. The CI will also have access to unblind participants at all sites. The date, reason and result will be documented and signed by the person carrying out the unblinding. This will be stored in a sealed envelope in the ISF. Disclosure of the unblinding result will be to individuals involved in the participant's care only. Where possible, the participant will remain blinded and remain in the trial and continue with the trial procedures. The Sponsor will be notified of any emergency unblinding occurring. In addition, a paper copy of the allocation will be stored securely in NHS Tayside Clinical Trials Pharmacy.

7.6. Baseline data

Baseline data will be collected at day 0 as per Schedule of Procedures, Appendix 4, and as described below, section 7.7.

7.7. Trial assessments

- Trial assessments will be performed according to the Schedule of Procedures, Appendix 4. Where trial assessments identify any clinically significant incidental findings, these will be communicated to the participant's GP, with the participant's consent.

Trial assessments will be carried out according to trial specific processes described in training documents.

Missed trial assessments or visits completed outside the visit window will not be reported as breaches where this is due to participant choice or a clinical decision. Excursions will be documented, and trial statistician made aware of discrepancies.

Demographics: Age, sex at birth, ethnicity.

Medical history: Focused medical history, taken from medical records and participant reporting, including the following information:

- Medical history required to confirm eligibility.
- History and diagnosis of HF including aetiology, if known.
- History and diagnosis of diabetes and diabetes-related complications including previous ketoacidosis, severe hypoglycaemia and microvascular complications (retinopathy, nephropathy and neuropathy).
- History of chronic medical conditions related to inclusion and exclusion criteria.
- Medication allergies.

Review of concomitant medications and therapies: taken from medical records and participant reporting. Participants are expected to be on optimal heart failure therapy as judged by their treating clinician and remain on stable doses of these throughout the duration of the trial.

NYHA class:

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

Review of adverse events (AE): participants will be asked about the occurrence of any AEs since the previous visit. Medical records will also be reviewed.

Height, weight, waist circumference and hip circumference.

Blood Pressure and pulse: seated recording.

Physical examination: a detailed physical examination will be performed at screening to exclude participants with co-morbidities or other clinical disorders that would constitute an exclusion from the trial. This will include the following systems:

- Respiratory
- Cardiovascular
- Abdominal
- Neurological

Electrocardiogram (ECG): A 12-lead ECG will be performed according to standard guidelines for determination of heart rhythm (sinus or atrial fibrillation or other e.g. paced) at screening.

Echocardiography: If an echocardiogram has not been performed within 24 months of screening a 2-dimensional transthoracic echocardiogram will 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 management, blood glucose management, diabetic ketoacidosis and hypoglycaemia: see section 7.8.

6-minute walk test: This test assesses the distance (in metres) an individual can walk in 6 minutes. The participant walks back and forth along a marked walkway of 20 meters at their own pace.

Urine pregnancy test: will be carried out for women of childbearing potential (WOCBP), as described in section 8.11. See also notes in section 8.11, regarding contraception.

Urine sample: A urine sample will be obtained for measurement of albumin, creatinine and sodium. Collected, processed, and stored as per laboratory manual. Additional optional urine samples at baseline and 16 weeks will be collected for future research dependent on participants consent.

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. NT-proBNP at baseline and week 16 and C-peptide at baseline will be stored frozen and shipped to Dundee for analysis for trial outcomes. Additional optional blood samples at baseline and 16 weeks will be collected for future biomarker research dependent on participants consent, see section 7.2.1. A maximum of 60 ml of blood will be obtained at any visit.

7.7.1. CMR sub-study assessments

Sub-study assessments will be performed according to the Schedule of Procedures, Appendix 4.

Height and weight

Full blood count (FBC): to be obtained at the time of the scan to permit measurement of extracellular volume. If it is not possible to obtain blood samples at time of scan, the FBC result from the main trial screening visit and/or week 16 visit will be used.

Cardiac MRI scans: To aid reproducibility, the CMR protocol should be constant for each participant. The participant should undergo CMR on the same scanner using the same acquisition protocol. Imaging may be performed at 1.5 Tesla or 3.0 Tesla field strength using a standard (e.g. 30-elements including 3 body and 2 spine) phased-array cardiac surface coil.

Participants will be advised to avoid caffeine containing drinks for 24 hours prior to the CMR examination. Wherever feasible, the CMR scan will be performed at approximately the same time of day on both occasions i.e. morning or afternoon.

The CMR scan will last approximately 1 hour. The participant will be given instructions regarding breath-holding and reassurance about the scan, particularly in relation to adenosine administration, prior to each scan.

Participants will have 2 intravenous cannulas inserted (one in each arm, for adenosine and gadolinium contrast administration).

During the scan injections of intravenous gadolinium contrast (up to 0.2 mmol/kg) and adenosine (up to 210mcg/kg/min) will be given. The participant will be given notice before any injections, and reassurance throughout the 2-3 minute duration of intravenous adenosine administration.

If a participant has had an adenosine stress CMR exam within 6 months of the baseline visit this can be used as the baseline scan if there has been no significant clinical change in the opinion of the local investigator

If CMR is not performed by the visit 3 window, then the visit 7 exam will not be performed.

The CMR will be reviewed by a trained reporter (e.g. a cardiologist or radiologist). Formal reporting will be performed as per local protocols. Participants will be informed of any clinically important findings in a timely fashion.

Heart rate, blood pressure: will be measured at rest prior to scan and during adenosine administration.

ECG monitoring: will be carried out during scanning as per routine CMR.

7.8. Review and recording of insulin management, blood glucose management, diabetic ketoacidosis and hypoglycaemia:

The majority of patients in the UK are provided with CGM systems (e.g. Flash CGM, Dexcom, Guardian) and capillary beta-ketone meters as standard care. Participants will all be provided with medical alerts (such as the STOP-DKA wallet card (see Appendix 6)) and where they don't already have them, blood ketone meters. In addition, some participants may have access to continuous ketone monitors during the trial. These will be supplied to all eligible trial participants, if available. A review of glucose and ketone management will be performed at each trial visit after screening by a local investigator or delegate. Review of glucose and ketone management may be delegated to an appropriately trained member of staff, for example a Specialist Diabetes Nurse. The final decision on management of glycaemic control and ketone management will be taken between the local investigator or delegate and the participant, however guidance is given here.

Participants should be managed in accordance with the recently developed position statements of the Association of British Clinical Diabetologists[39] and the International Consensus approach.[40] All participants will be carefully monitored throughout the trial and insulin dose adjustments made under the supervision of the research team as described below.

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.

Insulin Management:
Once randomisation is complete, individuals with an HbA1c <58mmol/mol at screening will have a 10% insulin dose reduction prior to taking their first dose of sotagliflozin/placebo. No reduction in insulin dose will be made for those with HbA1c ≥58mmol/mol at screening. All participants will then be advised to monitor regularly and to adjust insulin doses every 24-48 hours to achieve recommend blood glucose targets.

The total, basal and bolus doses of insulin used will be recorded for analysis for the 7 days prior to the trial visits at randomisation, week 4 and week 16.

Blood glucose management:
All participants will use CGMs that are supplied in the UK as standard care and data from these will be assessed at each visit by the local investigator or delegate. Participants who do not wish to use CGM will not be eligible to participate in the trial.

Where participants have a compatible CGM they will be asked if they wish to sign-up to free to use 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. Consent will be sought to share summary data from these reports and/or CGM recordings with the trial investigators. Participants who do not wish to sign-up to one of these apps will not be excluded from participating in the trial.

Investigators will 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.

CGM data will be entered into the data management system for trial analysis for the 2 weeks prior to the trial visits at randomisation, week 4 and week 16. Where available LibreView/Clarity etc. summary data will be used. The variables collected will include:

- Number of days CGM worn
- Percentage of time CGM is active
- Mean glucose
- Glycaemic variability (%CV).
- Percentage time in target, time above target and time below target.

Diabetic ketoacidosis (DKA):
Participants with type 1 diabetes should be aware of diabetic ketoacidosis. Further information on how to prevent, recognise, and treat DKA will be provided along with educational prompts. Participants will be also 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 will be provided with contact details of the local research team and relevant emergency contacts for advice should any of these situations occur.

In addition to the above monitoring, participants will be advised to perform additional ketone testing if capillary/CGM glucose is >11.1mmol/L for >2 hours or if feeling sick, according to standard sick day rules for diabetes management. Participants will be advised to check blood ketones if feeling unwell even when the capillary glucose levels are not particularly 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 will be encouraged to document reasons (e.g., alcohol, recent illness) for this and how it was managed. Advice will also be given regarding other times to check ketone levels (e.g., guidance is also given in Appendix 6 STOP-DKA protocol)[41]. Participants may be given a copy of the STOP-DKA guidelines, or local guidelines, dependent on local investigator's preference.

In summary the following strategies will be used to minimise DKA risk in addition to the educational measures:

- Participants will be asked to perform capillary ketone testing 4 times per day, 3 days before and 3 days after initiation of active drug/placebo, and 2 hours after changing each insulin giving set for those on insulin pump therapy as described earlier.
- Risk mitigation strategies, e.g. following the STOP-DKA Protocol if feeling sick or unwell with symptoms suggestive of impending DKA.

DKA will be defined as: blood ketone >3.0 mmol/l **and** blood pH of <7.3 or a bicarbonate <18mmol/l.

Hypoglycaemia:
Hypoglycaemic events during the trial will be defined and documented as the following:

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). **or** CGM less than 3.9 mmol/L (70 mg/dL) but greater than or equal to 3.0 mmol/L (54 mg/dL) for at least 15 minutes
Level 2 hypoglycaemia (moderate)	Measured plasma/capillary glucose concentration less than 3.0 mmol/L (54 mg/dL). **or** CGM < 3.0 mmol/L for at least 15 minutes

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 neuroglycopenia 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 will be asked to record the following:

- All level 2 and 3 hypoglycaemic events
- All symptomatic hypoglycaemia events for 2 weeks before baseline and at 14-16 weeks

7.9. Long term follow-up assessments

Nil

7.10. Quality of life assessments

KCCQ: a 23-item questionnaire measuring symptoms, physical and social limitations, and QoL in patients with heart failure. Scores range from 0-100 with lower scores representing worse quality of life.

DTSQ Status and Change: Assesses patient-reported outcomes related to their diabetes treatment. Includes eight items, and responses are scored on a 7-point scale, from +6 to 0. The scores of six items (satisfaction with current treatment, convenience, flexibility, understanding of diabetes, recommend treatment to others and willingness to continue) are added together to give the overall treatment satisfaction score (range +36–0), with higher scores denoting greater treatment satisfaction. The perceived frequencies of hyperglycaemia and hypoglycaemia are also assessed, rated on a scale of +6 (“Most of the time”) to 0 (“None of the time”). The DTSQ status version will be used at baseline and 16 weeks, while the DTSQ change version will also be performed at 16 weeks. This is a focused version of the questionnaire designed to overcome potential ceiling effects where respondents score near-maximum satisfaction at baseline and therefore have little room for improvement at follow-up.

EQ-5D-5L: A generic measure of QoL that can be used for multiple patient groups across different conditions. Patients will perform the EQ-5D-5L at baseline and 16 weeks.

7.11. Withdrawal criteria

Participants are free to withdraw at any time and are not obliged to a give reason(s). However, the CI, PI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow-up, while fully respecting the individual’s rights.

The investigator may withdraw a participant at any time if it is in the best interest of the participant and treatment continuation would be detrimental to the participant’s wellbeing. The Investigator will make a clinical judgment as to whether an AE is of sufficient severity to require

the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end-of-trial assessment.

A full explanation will be provided. As the trial is being conducted on an intention to treat basis, if the participant has been randomised and given one or more doses of IMP, s/he will be asked to complete trial visits as per the protocol, to allow for an intention to treat analysis – but will be censored in the per-protocol analysis. Participants are free to refuse to do so. Withdrawn participants will not be prescribed IMP.

Those withdrawn, including those lost to follow-up, will be identified and a descriptive analysis of them provided, including the reasons for their loss, if known, and its relationship to treatment and outcome.

7.11.1. Discontinuation of trial drug

The trial drug will be discontinued permanently in the following circumstances:

- Recurrent (more than 2) level 3 hypoglycaemia events with no other contributing factors, e.g. diet or exercise.
- DKA requiring hospitalisation.
- Renal failure requiring dialysis.
- Pregnancy.
- Diagnosed Fournier's gangrene.
- Circumstances where the PI feels that continuation of trial drug will be detrimental to the participant's well-being.

Where the participant, for whatever reason, permanently discontinues the trial drug they will be encouraged to remain in the trial completing all follow-up visits and calls.

7.11.2. Temporary discontinuation of trial drug

The trial drug will be temporary discontinued in the following circumstances:

- Potential DKA: Participants will be instructed to stop their trial drug if blood ketones are >1.5mmol/L. Restarting of the trial drug is at the discretion of the local investigator, however it is anticipated that this will not be restarted until ketones are <0.6mmol/L and symptoms (if present) have resolved.
- Clinically significant volume depletion (as judged by the local investigator) or intercurrent illness may necessitate a temporary cessation of trial drug, although additional steps should be taken initially as appropriate such as increasing fluid intake, adjusting loop diuretic dose.
- Suspected Fournier's gangrene.
- If the patient has stopped trial drug for >5 consecutive days, the PI should be notified to confirm that it is appropriate to restart the trial drug on a case-by-case basis.

7.12. Storage and analysis of clinical samples

Research samples including for NT-proBNP at baseline and 16 weeks and C-peptide at baseline will be stored locally and transferred to UoD, Division of Molecular and Clinical Medicine for analysis and storage either at the end of site participation or sooner if site requests.

Optional samples collected for future use will be stored locally and transferred to the UoD, Division of Molecular and Clinical Medicine either at the end of site participation or sooner if site requests. These samples will be registered with the Tayside Biorepository, part of the NHS Biorepository Network, and handled in accordance with the Human Tissue Act 2004 and the 2006 Human Tissue (Scotland) Act. The samples will remain under the control of the CI for use in future, ethically approved, research within the UoD and with other research collaborators (commercial and non-commercial). Access to the samples will be via application to the CI. Trial data may be released with samples as per section 7.2.1.

The collection, processing, storage and transfer of samples will be detailed in the Laboratory Manual. The analysis of samples will be detailed in the Laboratory Analytical Plans.

7.13. End of trial

The end of trial at all sites is defined as last participant last visit. The Sponsor, CI and/or the TSC have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, Research Ethics Committee (REC) Medicines and Healthcare products Regulatory Agency (MHRA) and National Health Service Research & Development (NHS R&D) Office(s) within 90 days, or 15 days if the trial is terminated prematurely. The PI will be responsible for arranging any appropriate follow-up for their participants.

A final clinical trial report will be published and the MHRA informed within 1 year of the end of the trial and will also be provided to the Sponsor and REC.

8. TRIAL TREATMENTS

8.1. Name and description of investigational medicinal product(s)

IMP	Dosage, form and strength	Placebo	Dosage, form and strength
Sotagliflozin	200mg oral tablet	matched	200mg oral tablet

8.2. Regulatory status of the drug

Sotagliflozin was approved for use in the UK by NICE at a dose of 200mg once daily in individuals with type 1 diabetes, BMI ≥27kg/m2 and taking insulin dose ≥0.5 units/kg body weight (Technology Appraisal TA622).

Sotagliflozin does not have a marketing Authorisation in the UK.

Sotagliflozin (Inpefa) was recently approved for use in the United States of America by the Food and Drug Administration in all patients with HF without limitations on use in individuals with type 1 diabetes.

8.3. Product Characteristics

The reference safety information (RSI) is described in Section 9.4.

8.4. Preparation and labelling of Investigational Medicinal Product

IMP and placebo tablets will be supplied to Clinical Trial Pharmacies in bottles labelled with annex 13 compliant labels. Bottles will be fitted with child-proof caps. Further details will be provided in the Pharmacy Manual.

8.5. Drug storage and supply

Trial drug will be stored at each site's Pharmacy/Clinical Trials Pharmacy securely between 15^{o}C and 30^{o}C, away from direct sunlight. Further details will be provided in the Pharmacy Manual.

8.6. Accountability Procedures

All IMP will be supplied by Lexicon Pharmaceuticals and labelled, Qualified Person released and distributed to sites by Sharp Clinical Services. Trial drug will be received by a delegated person at the trial site Clinical Trial Pharmacy, handled and stored safely and properly, and kept in a secured location as detailed in the Pharmacy Manual. All trial clinical supplies will be dispensed only in accordance with the protocol and Pharmacy Manual.

The PI or delegated trial staff will maintain an accurate record of the receipt and dispensing of the IMP. Monitoring of drug accountability will be performed as per Sponsor Monitoring Plan.

8.7. Dosage schedules

Participants will take one 200mg tablet of Sotagliflozin/matched placebo daily for a total of 16 weeks, usually before breakfast. If the participant misses a dose of the trial drug by less than 6 hours, they should still take it when remembered and then continue all subsequent doses as scheduled. If a participant misses a dose by more than 6 hours after it was scheduled then they should skip that dose and only take their next dose at their next scheduled time (i.e. the next day before breakfast).

8.8. Dosage modifications

No routine dose modification is planned during the trial. Participants will remain on a single dose of sotagliflozin 200mg daily or matched placebo throughout the trial.

8.9. Known drug reactions and interaction with other therapies

Insulin: may increase the risk of hypoglycaemia, see section 7.8 for mitigation of risk and insulin dose adjustments.

UGT enzyme inducers e.g. phenytoin, ritonavir, rifampicin: may decrease efficacy of sotagliflozin. Blood glucose management will be reviewed at each visit.

Digoxin: increase in $AUC_{0\text{-}mf}$ and C_{max} of digoxin. If digoxin toxicity is clinically suspected appropriate clinical action will be taken. This is likely to include checking digoxin levels.

Sotagliflozin may increase exposure of rosuvastatin, fexofenadine, paclitaxel, bosentan, methotrexate, furosemide, benzylpenicillin. It should be evaluated if additional safety monitoring is needed.

CYP2C9, CYP2B6 and CYP1A2: substrates of these enzymes should be monitored for decreases in their efficacy.

8.10. Concomitant medication

Details of all concomitant medications will be recorded on the trial eCRF on a concomitant medications log.

Other SGLT2 inhibitors are not permitted during the trial.

8.11. Trial restrictions

Patients should not be on a ketogenic diet.

WOCBP must be willing to have pregnancy testing prior to trial entry and prior to start of trial drug.

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause (including use of hormone replacement therapy).

In addition, WOCBP must be willing to use a form of a medically approved birth control method throughout the trial (and for minimum of 16 weeks after last dose), which include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- male condom
- sexual abstinence, when this is in line with the preferred and usual lifestyle of the participant, abstinence is acceptable only as true abstinence. Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Men who are sexually active with WOCBP will also be required to use a form of medically approved birth control method as listed above throughout the trial (and for minimum of 16 weeks after last dose) and will be requested to inform the trial team of any pregnancy occurring.

8.12. Assessment of compliance with treatment

Adherence to trial drug will be checked by tablet counting at visit 7. Participants will also be asked at each visit regarding their adherence to taking the trial drug daily.

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a consented participant which is not necessarily caused by or related to a medicinal product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between a trial drug and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial drug qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the summary of product characteristics (SmPC). It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event. Assessment of severity of AR: Mild: A reaction that is easily tolerated by the trial participant, causing minimal discomfort, and not interfering with everyday activities. Moderate: A reaction that is sufficiently discomforting to interfere with normal everyday activities and may warrant intervention. Severe: A reaction that prevents normal everyday activities or significantly affects clinical status and usually warrants intervention.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

	NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the SmPC for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other IMP, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Causality assessment

Unrelated	Where the AE is not considered to be related to the trial drug.
Possibly	Although a relationship to the trial drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication, or temporal relationship make other explanations more likely. Information on drug withdrawal may be lacking or unclear.
Probably	The temporal relationship and absence of a more likely explanation suggest the event could be related to the trial drug. Information on drug withdrawal may be available and if so the observed response to trial drug withdrawal is considered clinically reasonable
Definitely	The known effects of the trial drug or its therapeutic class, or based on challenge testing, suggest that the trial drug is the most likely cause. Information on drug withdrawal is usually available and the observed response to trial drug withdrawal is considered clinically reasonable and has a plausible temporal relationship to trial drug exposure

9.2. Operational definitions for (S)AEs

Worsening of glycaemic control, including hypoglycaemia and DKA during the trial will not be classed as an AE but are defined as outcomes. However, any events requiring hospitalisation or resulting in death, will be recorded as AEs and classified as SAEs.

Clinically significant volume depletion (as judged by the local investigator) or intercurrent illness requiring a temporary cessation of study drug will be recorded as an AE.

An abnormal laboratory finding, that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant, will be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition will be reported (e.g. renal failure, haematuria) not the laboratory abnormality. Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention will not be reported as AEs

A non-clinically significant, in the opinion of the investigator, worsening of a pre-existing condition during the trial will not be classed as an AE. Pre-specified elective hospitalisations for treatment planned prior to randomisation will not be considered as an AE. However, any AEs occurring during such hospitalisations will be recorded.

9.3. Recording and reporting of SAEs, SARs AND SUSARs

All AEs will be recorded on the AE Log in the eCRF. Details of AEs will be recorded in the participant's medical record. AEs will be assessed for severity and causality by the PI or delegate. AEs will be recorded from the time a participant consents to join the trial until the participant's last trial visit. Any SUSAR, that the investigator becomes aware of, will be reported to the Sponsor irrespective of how long after trial treatment administration the reaction has occurred.

Assessment of severity:

Mild: An event that is easily tolerated by the trial participant, causing minimal discomfort, and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities and may warrant intervention.

Severe: An event that prevents normal everyday activities or significantly affects clinical status and usually warrants intervention.

An AE may be classified as a SAE or AR.

Participants with unresolved AEs/SAEs at end of trial will be followed up until 30 days after participant's last visit. SUSARS will be followed until resolution, where a participant agrees to this.

The CI, PI or delegate will ask about the occurrence of AEs and hospitalisations at every visit during the trial. SAEs will be submitted to the Sponsor Pharmacovigilance Section via the online Tayside Pharmacovigilance System within 24 hours of becoming aware of the SAE. Site PIs will also notify the CI when submitting an SAE.

The evaluation of expectedness will be made based on the knowledge of the reaction and the relevant safety information (RSI) see Section 9.4. The Sponsor will make the assessment on expectedness.

The Sponsor is responsible for reporting SUSARs to the MHRA and the REC. Fatal or life-threatening SUSARs will be reported within 7 days and non-fatal and non-life threatening SUSARs within 15 days.

Reporting of safety data to the funders will be as detailed in the funding agreement.

9.4. Reference Safety Information

The current version, of the Investigator Brochure (IB) will be held in the TMF - specifically in Pharmacy Site File, Investigator Site File (ISF) and Sponsor File. IB Section 6.0 contains the Reference Safety Information for IMP. The IB will be reviewed at least annually and where there have been any changes to the Reference Safety Information which may impact on the trial the protocol will be reviewed and a substantial amendment submitted for regulatory approvals.

Mitigation of risks is detailed in Appendix 1.

9.5. Responsibilities

CI/PI or delegated staff:

- Checking for AEs and ARs at all visits.

CI/PI or medically qualified delegate:

- Confirmation of eligibility criteria
- Using medical judgement in assigning seriousness, causality and whether the event/reaction was related.
- Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

CI:

- Central data collection of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.
- Clinical oversight of trial participant safety, including an ongoing review of the risk / benefit.
- Immediate review of all SUSARs.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
- Periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.
- Preparing the clinical sections and final sign-off of the Development Safety Update Report (DSUR).
- Reporting safety information to funder and Lexicon as per contract.

Sponsor (University of Dundee/NHS Tayside):

- Expedited reporting of SUSARs to the MHRA and REC within required timelines.
- The unblinding of a participant for the purpose of expedited SUSAR reporting.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Lexicon Pharmaceuticals:

- Responsible for maintaining IB and the manufacturing/preparation documentation.

9.6. Notification of deaths

All deaths occurring during the trial, will be reported to the Sponsor irrespective of whether the death is related to disease progression, the trial drug or an unrelated event. Deaths will be reported to Sponsor as SAEs as per Section 9.3.

9.7. Pregnancy reporting

Pregnancy itself is not considered an AE or SAE, unless there is a congenital abnormality or birth defect. Any unexpected pregnancy occurring during the trial and the outcome of the pregnancy, will be recorded on a TASC Pregnancy Notification Form, and submitted to the Sponsor Pharmacovigilance Section tay.pharmacovigilance@nhs.scot within 24 hours of becoming aware of the pregnancy and the outcome of the pregnancy. The pregnancy will be followed up until the end of the pregnancy. If the trial participant is a male, informed consent for follow-up will be sought from his female partner.

9.8. Overdose

An overdose is defined as receipt of over 800mg of sotagliflozin at once. Multiple doses of 800 mg once daily were administered in healthy volunteers and these doses were well tolerated.

In the event of an overdose, appropriate supportive treatment will be initiated as dictated by the participant's clinical status.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE section in the eCRF. Any dose administered other than prescribed dose for that participant will be reported to the Sponsor as a protocol breach.

If an overdose of trial drug occurs during the trial, then the Investigator or other site personnel will inform the appropriate Sponsor representatives immediately, or no later than 24 hours after becoming aware of it. The designated Sponsor representative will work with the Investigator to ensure that all relevant information is provided to the Sponsor's Pharmacovigilance Committee.

9.9. Reporting urgent safety measures

The PI or other trial physician will take appropriate immediate urgent safety measures to protect the participants against any immediate hazard to their health or safety. The MHRA, REC and Sponsor will be notified in writing within three days.

9.10. The type and duration of the follow-up of participants after adverse reactions.

All ARs will be recorded as per section 9.3. Where ARs occur, assessment of clinical condition and appropriate treatment will be instigated by a delegated doctor and will continue until the symptoms resolve or the condition stabilises.

9.11. Development safety update reports

The DSUR will be prepared jointly by the Sponsor Pharmacovigilance Section and CI and submitted by the Sponsor to the MHRA on the anniversary of date of Clinical Trial Authorisation.

The DSUR and reports of SUSARs will be sent to REC by the Sponsor Pharmacovigilance Section. Any other safety reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

The sample size calculation was informed by the recent DEFINE-HF[31] trial of dapagliflozin vs. placebo in participants with symptomatic HF with reduced ejection fraction and type 2 diabetes or no diabetes, in which dapagliflozin caused an improvement of 4.7 points in the KCCQ Clinical Summary Score (SD 13.7) compared to placebo. To achieve 80% power to identify this difference at an alpha of 0.05, 268 participants (134/group) are required. Accepting the potentially greater attrition in a type 1 diabetes population a ~15% trial dropout will be allowed for and therefore it is planned to recruit 320 individuals. An improvement of ~5 points in KCCQ is accepted as a clinically important difference[29] and is certainly consistent with that seen in SGLT2i HF trials (Table 2), for example PRESERVED-HF[32], in which individuals with HFpEF were recruited and the magnitude of improvement in KCCQ was even larger than in DEFINE-HF (5.8 points). The KCCQ Clinical Summary Score is accepted for use in regulatory submissions to the FDA.

CMR sub-study sample size calculation

A recent study found that dapagliflozin caused a 50% increase in myocardial flow reserve measured using PET/CT.[44] In a predominantly non-diabetic cohort a 1SD increase in stress MBF (0.71 mL/g/min) was associated with a 54% relative risk reduction in MACE after a median of 20 months[47], while CMR-derived MPR is ~20% lower in T1D than in controls[48], so it is hypothesised that changes of these magnitudes in stress MBF and/or MPR could be clinically meaningful. To have 90% power to detect a 0.71 mL/g/min in stress MBF between sotagliflozin and placebo groups 44 participants are required, assuming balance in randomisation (22 per group).

10.2. Planned recruitment rate

Recruitment of 320 participants proceeding to randomisation is expected to take approximately 19 months across 10-15 recruiting sites. It is anticipated that the main cause of screen failures will be low NT-proBNP (~40% screen failure). Approximately 500 participants will therefore be required to be consented and attend for screening to achieve 320 participants randomised.

10.3. Statistical analysis plan

Statistical support will be provided by the TCTU trial statistician.

A statistical analysis plan will be developed prior to participant recruitment and will be finalised prior to data lock. Any deviations from this will be described and justified in the final report.

The statistical analysis plan will detail the summary of baseline data and flow of participants, primary and secondary outcome analysis, subgroup analyses, adjusted analysis, participant population and, procedure(s) to account for missing or spurious data.

Baseline demographic and clinical data will be described between sotagliflozin and placebo arms as mean +/- SD for continuous variables and number and percentage for categorical variables. Differences between arms will be compared using t-tests or chi-square tests as appropriate.

CMR sub-study statistical analysis

The CMR scans may be analysed during the course of the main trial, however, as unblinding will not occur until database lock for the main trial, the primary outcome of the sub-study will only be assessed at the same time as the main trial results are available. The primary analysis will be performed using mixed effects models on the intention-to-treat dataset adjusting for relevant variables. Changes in sub-study outcomes will also be compared to the main trial outcomes including change in KCCQ score and NT-proBNP.

10.3.1. Primary outcome analysis

The primary endpoint of change in KCCQ clinical summary score at 16 weeks will be analysed using mixed effect models adjusting for baseline KCCQ, age, eGFR and LVEF.

Statistical significance will be defined as a two-sided p value <0.05 for all tests.

10.4. Interim analysis and criteria for the premature termination of the trial

A blinded interim analysis (primarily for safety) will be performed and reviewed by the DMC, at a suitable time point (e.g., once 1/3 of the participants have completed the trial).

10.5. Participant population

The primary analysis will be by intention to treat (ITT), defined as all participants successfully randomised. Sensitivity analyses using both modified ITT (all randomised participants with at least one evaluable endpoint) and per-protocol data will also be performed.

10.6. Economic evaluation

No economic evaluation will be performed.

11. DATA MANAGEMENT

11.1. Data collection tools and source document identification

The PI or delegate will maintain source documents for each participant in the trial, consisting of hospital medical records containing demographic and medical information, laboratory data, electrocardiograms, trial questionnaires and the results of any other tests or assessments. The questionnaires will be completed by the participants and act as source data. The completed form will be filed in the ISF. All trial data relevant to a participant's general medical history will be recorded in the medical record. The medical record will be flagged to state that the participant is participating in the SOPHIST trial.

An eCRF, using CASTOR Electronic Data Capture system, will be provided by TCTU. The trial system will be based on the protocol for the trial and sub-study. Development and validation of the trial database and quality control will be done according to TCTU procedures. The eCRF will not collect more information than is required to meet the aims of the trial, sub-study and to ensure the eligibility and safety of the participant.

The PI may delegate eCRF data entry but is responsible for completeness, plausibility, and consistency of the eCRF. Delegated trial staff will enter the data required by the protocol into the eCRFs following database training. Any queries will be resolved by the PI or delegated member of the trial team. On completion of data collection, the PI must certify that the data entered are complete and accurate.

Data verification, cleaning and extraction will be performed as per TCTU local procedures and detailed in the trial-specific Data Management Plan.

All electronic data will be stored on secure UoD or cloud-based servers which have restricted access and have disaster recovery systems in place.

CMR sub-study data collection

CMR DICOM files from other participating sites will be transferred to Dundee University via a secure transfer portal. The mNCA (site agreement) will act as the formal data transfer agreement between the relevant parties to govern this transfer, ensuring compliance with applicable data protection and privacy regulations.

11.2. Data handling and record keeping

The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 2018. The Data Controller will be the UoD and the Data Custodian will be the CI.

Development and validation of the trial database, data quality control and data extraction will be managed by TCTU. Details will be documented in the trial-specific Data Management Plan.

11.3. Access to Data

The CI, PIs and all institutions involved in the trial will permit trial-related monitoring, audits, REC review, and regulatory inspection. In the event of an audit, the CI and/or PI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all trial records and source documentation.

Post database lock, unblinded aggregated data will be made available to Lexicon Pharmaceuticals using secure data transfer processes. Anonymised raw data sets may be made available to Lexicon Pharmaceuticals if required for FDA submission. Details of data access and transfer requirements will be included in a Data Transfer Agreement between UoD and Lexicon Pharmaceuticals.

11.4. Archiving

Archiving of trial documents will be in compliance with Sponsor Standard Operating Procedures. Medical records will be maintained in compliance with local NHS policy on retention of medical records. The CI will be responsible for arranging the archiving of the TMF and ensuring that research data is archived in a way that will permit accurate reconstruction of the research. Sites will be responsible for archiving local trial records including the ISF and Pharmacy Site File. Sponsor will be responsible for archiving the Sponsor file.

12. MONITORING, AUDIT & INSPECTION

12.1. Monitoring

A trial risk assessment will be carried out by the Sponsor prior to Sponsorship approval being granted. The Sponsor will determine the appropriate extent and nature of monitoring for the trial and will appoint appropriately qualified and trained monitors. A Monitoring Plan will be developed by the Sponsor based on the trial risk assessment which will include on site and/or remote monitoring. The Monitoring Plan will be reviewed regularly using a risk-based approach and updated as required. The Monitoring Plan will detail the procedures and anticipated frequency of monitoring and processes reviewed. Sites must have access to source data for purposes of remote monitoring and assist the Sponsor in monitoring of the trial. In recognition that source data may come from different sources at each site, sites shall ensure that a source data identification list is supplied to the Monitoring Team in advance of any monitoring review and ensure this data is available on the agreed date and time to facilitate the review.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from an independent REC for the trial protocol, Informed Consent Form, and other relevant documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the TMF.

The CI will notify the REC of the end of the trial. If the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination. The CI will submit a final report with the results, including any publications/abstracts, according to REC approval conditions.

A copy of all REC reports will be submitted to the Sponsor.

13.2. Peer review

This trial has been funded by JDRF who have reviewed the grant application. The trial has also been peer reviewed by Lexicon Pharmaceuticals. The protocol has been reviewed and approved by the Sponsor Committee.

Resulting publications will be reviewed by the referees of the journal to which the paper will be submitted.

13.3. Public and Patient Involvement

The trial is being funded by JDRF a leading charity which supports research for people with type 1 diabetes, their involvement with patients and the public informs the design of trials they fund. The collaborators have taken into account informal discussions with patients over the years to inform the design of the trial.

More specifically the following PPI activities are planned:

Patients have reviewed the Participant Information Sheet and lay summary, their feedback, where appropriate, has been taken into account, for example, provision of the brief Participant Information Sheet, removal of explanation of what hypos and diabetic ketoacidosis is and ensuring blood glucose and ketone measurement is minimised where possible to reduce burden.

The formation of a PPI group for input during the trial is in progress. It is hoped that at least one member of this group will attend the Research Ethics Committee application meeting and join the Trial Steering Committee meetings. Input from the PPI group will also be sought if there are any changes to the trial design or documents planned and for dissemination of the results.

13.4. Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation is obtained from the MHRA and favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol participants into the trial, the CI, PI, or delegate will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the trial, the CI, PI, or delegate, in agreement with the Sponsor, will submit information to the appropriate body for them to review and issue approval for the amendment. The CI, PI or delegate will work with sites so they can put the necessary approvals and arrangements in place to implement the amendment to confirm their support for the trial as amended.

13.5. Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed, e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Trial staff will not implement deviations to the protocol except where necessary to eliminate an immediate hazard to trial participants.

Accidental protocol breaches can happen at any time. They will be adequately documented on the relevant forms and reported to the CI and Sponsor using the TASC Breach Reporting Form. If there is a breach of the protocol, the nature of and reasons for the breach will be documented in the trial Breach Log. Breaches from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to affect to a significant degree –

a) the safety or physical or mental integrity of the participants of the trial; or

b) the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The Sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

a) the conditions and principles of GCP in connection with that trial; or
b) the protocol relating to that trial, as amended from time to time.

If a serious breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the Breach Reporting Form and will be recorded in the eCRF and documented in the trial Breach Log.

If a breach necessitates a subsequent protocol amendment, this will be submitted as per section 13.10.

13.7. Data protection and participant confidentiality

The CI and trial staff will comply with the requirements of the General Data Protection Regulation (EU) 2016/679 (GDPR) and the UK Data Protection Act 2018 or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data and will uphold the principles of GDPR in Article 5.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

All trial records and data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate data will have limited access measures via usernames and passwords. Age, gender, and ethnicity will be the only personal identifiable details held on CASTOR Electronic Data Capture system. Initials, date of birth and gender will be held on the TRuST system to allow for the identification of participants where emergency unblinding is required.

Personal data or data concerning health will not be released without the existence of a legal basis for processing under Articles 6 and 9 of GDPR, such as official authority 6(1)e or substantial public interest 9(2)g. The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated participant data will be restricted to Lexicon Pharmaceuticals, the CI and appropriate delegated trial staff. Lexicon Pharmaceuticals will not have access to personal identifiable details other than those held on the electronic data capture system. Anonymised participant data will also be available to interested parties after publication of the final report upon reasonable written request to the CI and subsequent approval.

The transfer of data to Lexicon Pharmaceuticals will be as described in the Clinical Research Agreement.

Published results will not contain any personal data that could allow identification of individual participants.

13.8. Financial and other competing interests for the Chief Investigator, PIs at each site and committee members for the overall trial management

At the time of writing the protocol the investigators report no relevant conflicts of interest. Detailed disclosure information, if any, will be collected at site initiation and documented in the site file.

13.9. Indemnity

The UoD and Tayside Health Board are Co-Sponsoring the trial.

Insurance. – The UoD will obtain and hold Clinical Trials Insurance cover for legal liabilities arising from the trial.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which covers the legal liability of Tayside in relation to the trial.

Where the trial involves UoD staff undertaking clinical research on NHS participants, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity. The Co-Sponsors do not provide trial participants with indemnity in relation to participation in the Trial but have insurance for legal liability as described above.

Where other Scottish Health Boards are participating as trial sites, those other Scottish Health Boards will maintain membership of CNORIS to cover their liability in relation to their conduct of the trial.

Other participating sites will maintain membership of a scheme similar to CNORIS.

13.10. Amendments

Amendments to the protocol will be conducted in compliance with Sponsor Standard Operating Procedures. The decision to amend the protocol will lie with the CI after consultation with the TMG, and trial statistician. The TSC will also be consulted on any major amendments. The CI will seek Sponsor approval for any amendments to the Protocol or other approved trial documents. The Sponsor will decide whether an amendment is substantial or non-substantial. The CI will be responsible for submitting the amendment to the appropriate regulatory authorities and communicating amendments to sites. Amendments to the protocol or other trial documents will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC and/or MHRA, as appropriate, and appropriate site approvals. The amendment history will be detailed in an Amendment Log.

13.11. Post-trial care

Following the end of trial, participants should be continued, started, or restarted on the appropriate treatment for their diabetes and HF. No provision for continuation of trial drug will be made by the trial team or Sponsor.

13.12. Access to the final trial dataset

The CI and Trial Statistician will have access to the final trial dataset. Access to the final trial dataset to others will be approved by the CI.

14. DISSEMINIATION POLICY

14.1. Dissemination policy

Details of the trial and clinical trial final report will be published on ISCTRN Registry, no later than 12 months after the end of trial. Trial results will be available to the public via the ISCTRN registry. The report will be made available to the Funder. The report can be used for publication and presentation at scientific meetings. Trial investigators have the right to publish orally or in writing the results of the trial.

Participants in the trial will be notified of the results via a Results Letter.

14.2. Authorship eligibility guidelines and any intended use of professional writers

The data arising from this trial resides with the trial team and ownership with the UoD. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial final report will be prepared.

Authorship and the publication will be defined and developed by the TSC and the site investigators. An inclusive approach will be taken with either named or group authorship (e.g. “on behalf the SOPHIST Investigators”). In the case of group authorship all contributing participants will be named in (for example) a supplementary appendix. Named authors will be expected to meet authorship criteria set out by the International Committee of Medical Journal Editors.

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16.1. Appendix 1 – Risk

Risks associated with trial interventions

☐ A ≡ Comparable to the risk of standard medical care

☒ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification:

As outlined in the table below and in the protocol, there are known risks with sotagliflozin in this group of patients (DKA, hypoglycaemia, volume depletion) that are greater than standard care. These are however known and the research team have introduced mitigations to manage these. This also is balanced against the likely benefit from SGLT2 inhibitors in patients with HF (and also in glycaemic control) that could lead to an improvement in clinical status. Overall the Sponsor therefore judges the risk to be somewhat higher that standard medical care.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?	
IMP	Body system/Hazard	Activity	Frequency
IMP	DKA	See section 7.8: Review of glucose management and DKA	At every visit
IMP	Hypoglycaemia	See section 7.8: Review of glucose management and DKA	At every visit
IMP	Genital/Urinary Tract Infections	Advice on risk of urogenital infection given at the randomisation visit as per standard initiation of SGLT2 inhibitors.	At randomisation
IMP	Fournier's Gangrene (necrotising fasciitis of the perineum)	Advice on risk of Fournier's Gangrene, the symptoms to watch for and the importance of seeking immediate medical attention if having these given at the randomisation visit as per standard initiation of SGLT2 inhibitors.	At randomisation and every visit afterwards

		Participants presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotising fasciitis. If suspected, should discontinue trial drug and start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement.	
IMP	Volume Depletion	Advice given regarding “sick day rules” as per the STOP-DKA protocol (appendix 6).	At every visit
IMP	Blood creatinine increased/ Glomerular filtration decreased and renal-related events	Careful attention to fluid status and signs and symptoms of dehydration.	Renal function at visits 3, 5 and 7; renal-related events at every visit
CMR (sub-study)	Gadolinium contrast - small risk of Nephrogenic systemic fibrosis (NSF) and rare hypersensitivity reactions.	Check if participant has any contra-indication to gadolinium contrast (e.g. previous contrast reactions and poor kidney function).	At screening and before each CMR.
CMR (sub-study)	Adenosine – common short-lived symptoms (maximum couple of minutes while infusion running) of chest tightness, shortness of breath or mild nausea. Rarely adenosine may induce arrhythmias, hypotension or bronchospasm, particularly in susceptible individuals such as those with asthma.	Check if participant has any contra-indication to taking this medication (i.e. asthma; severe chronic obstructive lung disease; decompensated heart failure; long QT syndrome; second- or third-degree AV block and sick sinus syndrome; severe hypotension). Monitoring of ECG, heart rate and blood pressure will be undertaken throughout the procedure.	At screening and before each CMR.

CMR (sub-study)	Non-CMR compatible implantable devices and/or metallic foreign bodies moving or heating up, causing injury or device malfunction.	Check if participant has any non-CMR compatible implantable devices and/or metallic foreign bodies.	At screening and before each CMR.
Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.) A DMC will be established to oversee the safety of trial participants. The DMC will be unblinded to allocation. The DMC will be provided with information on SAEs, hypoglycaemic events, DKA events and safety blood results. The DMC will decide frequency of meetings, it is anticipated that they will meet shortly after recruitment starts and every 4-6 months but at least annually.			
Outline any processes (e.g., IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach. Nil			

16.2. Appendix 2 - Trial management / responsibilities

Responsibilities will be detailed in the co-Sponsorship and participating site agreements.

16.2.1. Participant registration/randomisation procedure

TCTU TRuST web-based randomisation system will be used.

Sites will be provided with a randomisation guide detailing the web-based randomisation system process. Prior to recruitment, individuals delegated this task will be given an individual username and password upon completion of training.

16.2.2. Data management

Data management will be overseen by TCTU Data Management Team.

Local sites will be expected to enter data directly on to the eCRF. Worksheets will be provided to facilitate this process, but their use is not mandatory. Worksheets, where used, will not be used for monitoring purposes.

All data from participants should be entered on the eCRF within 7 days of the last data collection point for that participant.

Data queries will be generated by the Data Management Team and should be addressed at the earliest opportunity.

16.2.3. Preparation and submission of amendments

TCTU Trial Management Team will be responsible for working with the CI to submit any amendments.

16.2.4. Preparation and submission of Annual Reports

The Sponsor Pharmacovigilance Team will be responsible for liaising with the CI to submit DSURs.

16.2.5. Data protection/confidentiality

The CI and trial staff will comply with the requirements of the Data Protection Act 2018, GDPR and the Data Protection Act 2018, or any subsequent amendment or replacement thereof regarding the collection, storage, processing and disclosure of personal data. The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

16.2.6. Trial documentation and archiving

Archiving trial site data will be the responsibility of individual sites. Payment for archiving will be provided as per site agreement.

16.3. Appendix 3 – Authorisation of participating sites

16.3.1. Required documentation

The following data should be made available to TCTU Trial Management Team prior to site initiation:

- PI CV, signed and dated within the last 2 years
- PI GCP certificate
- Protocol signature page, signed and dated by PI
- Copy of signed Participating Site Agreement
- Copy of NHS R&D confirmation of capacity and capability

The following data should be made available and held within the ISF/Pharmacy Site File prior to site initiation:

- CV, signed and dated for all trial staff listed on Delegation Log
- GCP certificate for all trial staff listed on Delegation Log

16.3.2. Procedure for initiating/opening a new site

Site Initiation will be performed by Monitors and TCTU Trial Management Team and may be on site and/or remote.

TCTU Trial Management Team will initiate release of trial drug to the site after NHS R&D confirmation of capacity and capability.

16.3.3. Principal Investigator responsibilities

The PI's legal responsibilities will be listed in the Participating Site Agreement. A summary is given below:

- Attendance at the site initiation meeting
- Training of new members of trial staff in the protocol and its procedures,
- Ensuring that the ISF is accurately maintained
- Dissemination of important safety or trial related information to all stakeholders within their site
- Safety reporting within the required timelines
- Ensuring data entry to eCRF and responses to data clarification queries are completed within the required timelines
- Certify data entered on eCRF is correct and complete
- Ensuring any trial staff coming into contact with participants have the appropriate Personal Protective Equipment and training in its use
- Archiving of site trial data

16.4. Appendix 4 – Schedule of Procedures

	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	Remote/ Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site
Informed Consent	X							
Eligibility	X		X					
Demographics	X							
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, if required	X							
Review of Glucose Management including ketone check		X	X	X	X	X	X	X
Education for glucose and ketone management		X	X	X	X	X	X	X
Registration with app such as LibreView/Clarity etc. (if not already signed up), optional		X						
Documentation of summary Data and/or glucose readings from CGM, from previous 2 weeks			X		X		X	
Documentation of glucose and ketone readings		X	X	X	X	X	X	X
Documentation of hypoglycaemic and DKA events		X	X	X	X	X	X	X

	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	Remote/ Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site
KCCQ	X		X		X		X	
DTSQ (status at baseline, change and status at 16 weeks)			X				X	
EQ-5D-5L			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) if required	X							
NTproBNP for central lab analysis (Dundee)			X				X	
C-peptide for central lab analysis (Dundee)			X					
Urine albumin, creatinine, sodium			X		X		X	
Additional research bloods			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	

	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	Remote/ Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site	Research Site	Remote/ Research Site
Sub-study* **								
CMR scan	X						X	
Height and Weight	X						X	
FBC	X						X	
Heart rate and blood pressure	X						X	

*The timing of the echocardiogram can vary as long as results are available in time for confirmation of participant eligibility at visit 3.

**Dispensing may be delayed by up to 3 days to facilitate local practices. ***CMR sub-study assessments may not necessarily be performed on the same day as the rest of the visit due to scheduling, some variation in the timing of the scan is acceptable. CMR will be performed within the following timescales:

- Baseline CMR scan: Day -30 to day 0.
- Visit 7 (week 16) – End of treatment scan. This can be performed up to 7 days prior to and 7 days after the scheduled visit 7.

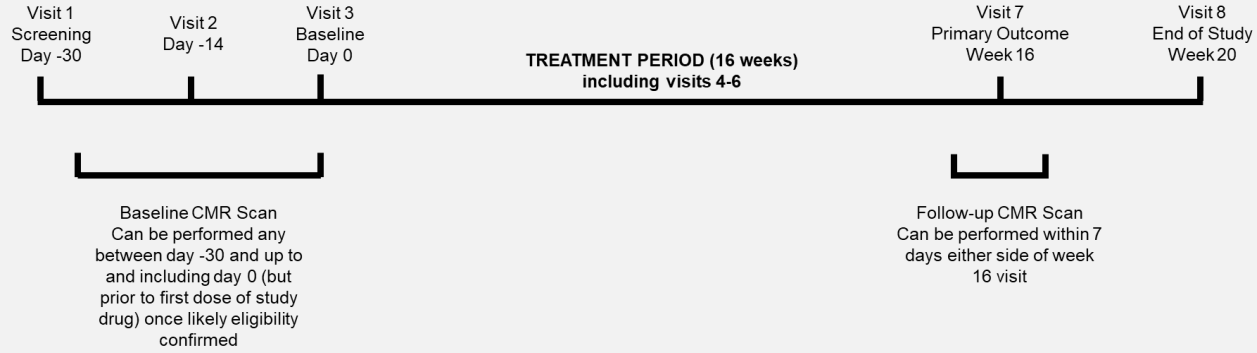


Figure 1. Timing of CMR in relation to the main trial visits.

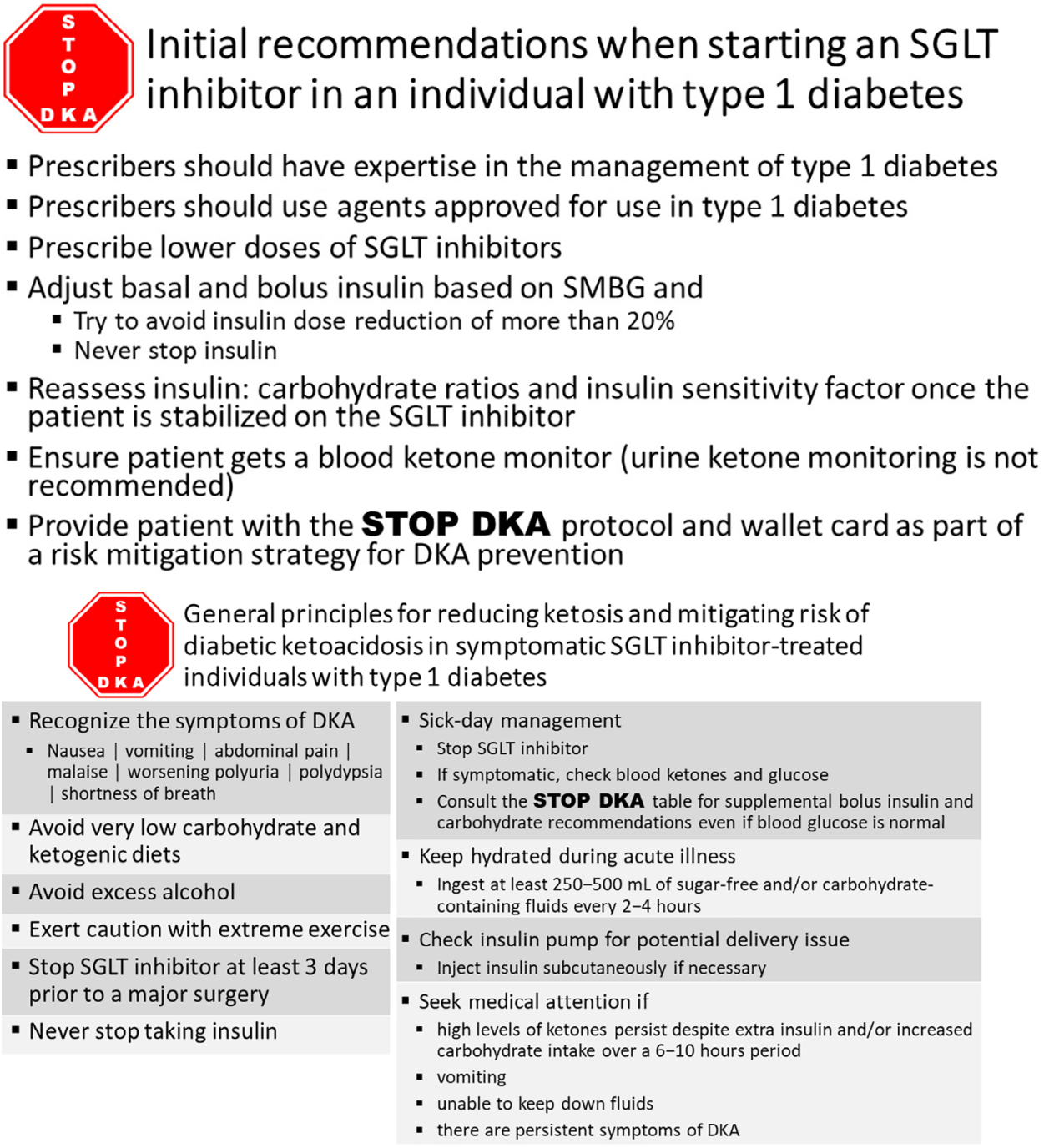
16.5. Appendix 5 – Safety Reporting Flow Chart

Activity	Responsibility	Timing	Comments
Review medical records and questioning of participant for evidence of AEs at all visits.	Trial staff	All visits	Recorded on eCRF system.
Review of recorded AEs for causality and seriousness	PI (or delegate)	Within 7 days of recording	Recorded on eCRF and/or medical records.
Reporting SAEs - All SAEs need to be assessed and signed off by the PI or delegated doctor.	PI (or delegate)	Within 24 hours of becoming aware of SAE	Reported via the online Tayside Pharmacovigilance system
Reviewing of SAEs	Sponsor	Within 24 hours of receiving SAE report	Pharmacovigilance Committee
Reporting of SUSARs to MHRA	Sponsor	Within 7 days if life threating or fatal. Within 15 days for others	Senior research Governance manager or delegate

16.6. Appendix 6 – STOP-DKA Protocol

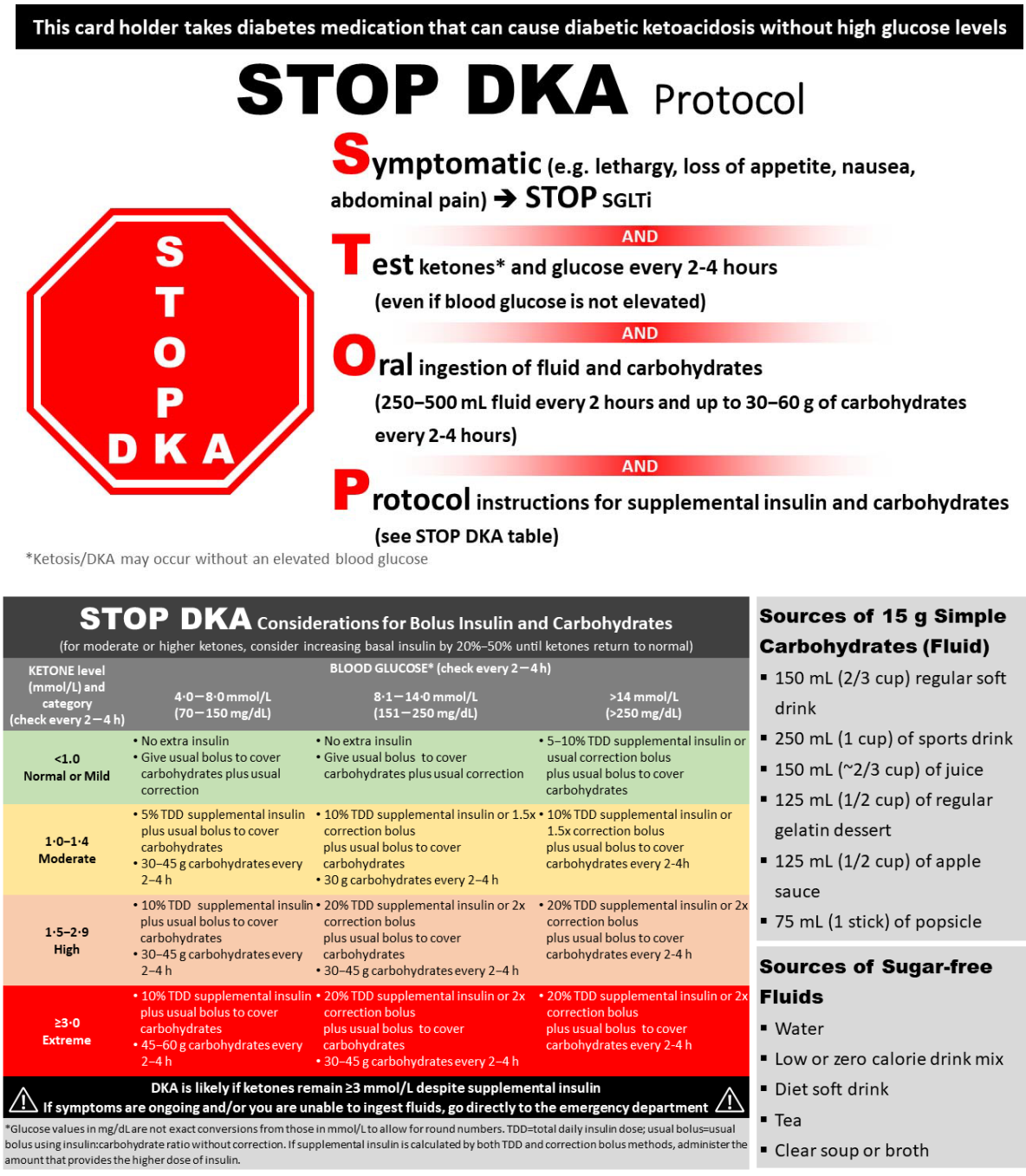
From Goldenberg et al. 2019[41]

The STOP-DKA protocol provides advice to clinicians that should be taken into consideration when starting sotagliflozin/placebo. This is simply provided for some general guidance that could be offered to participants but is not mandatory for use by sites. This is summarised in the figure below:



A 2-sided wallet card is available, reproduced below. This could be provided to participants in the trial.

STOP-DKA Wallet Card



This card holder takes diabetes medication that can cause diabetic ketoacidosis without high glucose levels

STOP DKA Protocol

Symptomatic (e.g. lethargy, loss of appetite, nausea, abdominal pain) ➔ **STOP** SGLTi

AND

Test ketones* and glucose every 2-4 hours
(even if blood glucose is not elevated)

AND

Oral ingestion of fluid and carbohydrates
(250–500 mL fluid every 2 hours and up to 30–60 g of carbohydrates every 2-4 hours)

AND

Protocol instructions for supplemental insulin and carbohydrates
(see STOP DKA table)

*Ketosis/DKA may occur without an elevated blood glucose

STOP DKA Considerations for Bolus Insulin and Carbohydrates

(for moderate or higher ketones, consider increasing basal insulin by 20%–50% until ketones return to normal)

KETONE level (mmol/L) and category (check every 2—4 h)	BLOOD GLUCOSE* (check every 2—4 h) 4·0—8·0 mmol/L (70—150 mg/dL)	8·1—14·0 mmol/L (151—250 mg/dL)	>14 mmol/L (>250 mg/dL)
<1.0 Normal or Mild	• No extra insulin • Give usual bolus to cover carbohydrates plus usual correction	• No extra insulin • Give usual bolus to cover carbohydrates plus usual correction	• 5–10% TDD supplemental insulin or usual correction bolus plus usual bolus to cover carbohydrates
1·0–1·4 Moderate	• 5% TDD supplemental insulin plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates • 30 g carbohydrates every 2–4 h	• 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates every 2-4h
1·5–2·9 High	• 10% TDD supplemental insulin plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h
≥3·0 Extreme	• 10% TDD supplemental insulin plus usual bolus to cover carbohydrates • 45–60 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h

⚠ **DKA is likely if ketones remain ≥3 mmol/L despite supplemental insulin**
If symptoms are ongoing and/or you are unable to ingest fluids, go directly to the emergency department ⚠

*Glucose values in mg/dL are not exact conversions from those in mmol/L to allow for round numbers. TDD=total daily insulin dose; usual bolus=usual bolus using insulin:carbohydrate ratio without correction. If supplemental insulin is calculated by both TDD and correction bolus methods, administer the amount that provides the higher dose of insulin.

Sources of 15 g Simple Carbohydrates (Fluid)

- 150 mL (2/3 cup) regular soft drink
- 250 mL (1 cup) of sports drink
- 150 mL (~2/3 cup) of juice
- 125 mL (1/2 cup) of regular gelatin dessert
- 125 mL (1/2 cup) of apple sauce
- 75 mL (1 stick) of popsicle

Sources of Sugar-free Fluids

- Water
- Low or zero calorie drink mix
- Diet soft drink
- Tea
- Clear soup or broth

16.7. Appendix 7 – Amendment History

Amendment No.	Protocol version no.	Date	Author(s) of changes	Summary of changes made
NA	2	28-02-2024	J. Rocha H. Watt M. Band I. Mordi.	Changes made as part of the response to the MHRA, REC and HRA assessments: Exclusion criteria updated Other minor clarifications
AM05	3	13-05-24	J. Rocha H. Watt M. Band I. Mordi A. Hapca M. Achison.	Clarification of inclusion and exclusion criteria Remove urine glucose and NYHA classification at visit 3 Change timing of HbA1c from visit 3 to visit 1 Other minor corrections and clarifications
AM09	4	25-09-24	J.Rocha	Change of timeframe for the review of AEs Other minor corrections and clarifications.
AM11	5	02-09-25	J.Rocha I. Mordi M. Band.	Integration of sub-study protocol, Fournier's Gangrene risk information and other minor clarifications/corrections.
AM12	6	31-11-25	I. Mordi M. Band.	Change to inclusion criteria Clarification of where sites can identify participants