Clinical Study Protocol	
Study Intervention	Dapagliflozin
Study Code	D169DC00001
Version	4.0
Date	23 Feb 2023

A Registry-based, Randomised, Double-blind, Placebo-Controlled Cardiovascular Outcomes Trial to Evaluate the Effect of Dapagliflozin on Cardiometabolic Outcomes in Patients without Diabetes with Acute Myocardial Infarction at Increased Risk for Subsequent Development of Heart Failure

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D169DC00001

Amendment Number: 3

Study Intervention: Dapagliflozin

Study Phase: 3

Short Title

Dapagliflozin in Patients without DM with acute MI

Acronym: DAPA-MI

Medical Monitor Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP v.4.0 (Amendment 3)	*23-Feb-2023*
CSP v.3.0 (Amendment 2)	*14-Dec-2021*
CSP v.2.0 (Amendment 1)	*25-May-2021*
CSP v.1.0 (Original Protocol)	*16-Apr-2020*

Amendment 3 23-Feb-2023
This is a substantial amendment based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:
In February 2023, the observed blinded primary endpoint event rate in the DAPA-MI study was substantially lower than anticipated. To maximize the scientific value of the study, without substantially increasing the sample size or prolonging the study duration, the primary endpoint and the primary analysis method were revised to evaluate the effect of dapagliflozin on a series of cardiometabolic outcomes, assessed as a hierarchical composite endpoint using a win-ratio analysis.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Protocol Title	To reflect the trial will evaluate the effect of dapagliflozin on cardiometabolic outcomes.	Changed to reflect the revised primary endpoint.	Substantial
1.1 Synopsis	To reflect the trial will evaluate the effect of dapagliflozin on cardiometabolic outcomes.	Changed to reflect the revised primary endpoint.	Substantial
1.2 Schema Figure 1	Study assumptions were updated.	To reflect the change in study description.	Substantial
2.1 Study Rationale	To reflect the trial will evaluate the effect of dapagliflozin on cardiometabolic outcomes.	Changed to reflect the revised primary endpoint.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
2.3 Benefit/Risk Assessment	To reflect the addition of cardiometabolic outcomes in the revised primary endpoint.	To reflect the revised primary endpoint.	Substantial
Table 3 Objectives and Endpoints	Objectives and endpoints were updated.	To reflect on how the study will be evaluated.	Substantial
4.1 Overall Design	To reflect hierarchical composite endpoint approach.	To reflect the revised primary endpoint.	Substantial
4.4 End of study definition	PACD was removed and the end of the study definition was re-defined.	To allow for patients to perform closure visits before all patients have been followed up 3 months.	Non-substantial
4.6 The Trial Registry Collaborators	To clarify MINAP access was not provided to hospitals in Scotland.	Due to revised study timelines.	Non-substantial
4.8 Study Committees	Efficacy interim analysis was removed.	Not applicable due to the revised primary endpoint.	Non-substantial
7.3 Lost to Follow up	PACD was removed and the definition of lost to follow-up was updated.	To align with the modified closure of the study.	Non-substantial
8.1 Efficacy Assessments	It was aligned with updated objectives and endpoints.	To reflect on how the study will be evaluated.	Substantial
8.3 Adverse Events and Serious Adverse Events	The reference was changed to the primary endpoint.	To align with revised objectives and endpoints.	Substantial
8.11 Unify™ Mobile Software Application	PACD was removed and the collection schedule with Unify app was updated.	To align with the modified closure of the study.	Non-substantial
9.1 Statistical Hypotheses	The efficacy interim analysis was removed	Previous assumption for interim analysis no longer applicable.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	and allocation of alpha was updated.		
9.2 Sample Size Determination	The sample size calculation was updated.	To align with the revised primary endpoint.	Substantial
9.4 Statistical Analyses	Primary and secondary endpoints assessments were updated.	To align with revised objectives and endpoints.	Substantial
9.5 Interim Analyses	Efficacy interim analysis was removed.	Previous assumption for interim analysis no longer applicable.	Substantial
Appendix A1 Regulatory and Ethical Considerations	Requirements for "Serious Breaches" was added.	The update was required to comply with regulatory and global company requirements.	Non-substantial
Appendix A6 Data Quality Assurance	Updated information about retention timelines of records and documents to [25 years after study archiving or as required by local regulations].	The update was required to comply with global company requirement.	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

A Registry-based, Randomised, Double-blind, Placebo-Controlled Cardiovascular Outcomes Trial to Evaluate the Effect of Dapagliflozin on Cardiometabolic Outcomes in Patients without Diabetes with Acute Myocardial Infarction at Increased Risk for Subsequent Development of Heart Failure

Short Title

Dapagliflozin in Patients without DM with acute MI

Rationale

Approximately 7 million individuals suffer a myocardial infarction (MI) annually, and survivors of MI remain at high risk for new major adverse cardiovascular (CV) events, CV death and for developing heart failure (HF) (Piepoli et al 2016). The development of HF following an acute myocardial ischaemia episode is strongly associated with incapacitating symptoms, poor functional status, reduced health-related quality of life and unfavourable long-term prognosis (Nieminen et al 2015, Nunez-Gil et al 2010) . HF is also one of the leading causes of all hospital admissions, generating substantial costs for health care systems. Therefore, MI therapies that could prevent the development of HF as well as reoccurrence of major CV events represent a large and unmet medical need.

Sodium glucose co-transporter 2 inhibition with dapagliflozin is associated with several known or postulated cardioprotective effects. In large outcome studies, treatment with dapagliflozin have been shown to prevent HF events and CV death in type 2 diabetes mellitus (T2DM) patients at high risk for, or with established atherosclerotic CV disease(Wiviott et al 2019), and it has also been confirmed that dapagliflozin constitutes an effective treatment option in patients with established HF and reduced ejection fraction with and without T2DM (McMurray et al 2019). Observations from mechanistic studies have demonstrated multifaceted CV protective effects of dapagliflozin including influence on cardiac loading conditions (ie, reduced preload and afterload) (Lan et al 2019), energy substrate utilisation and left ventricular remodelling processes ─ which may also be of clinical benefit in the early phase after a MI (Lahnwong et al 2018; Santos-Gallego et al 2019).

This study will evaluate the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to Standard of Care (SoC) therapies for patients with MI, for the prevention of hospitalisation for HF (HHF) or CV death.

In February 2023, the study was revised to evaluate the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to Standard of Care (SoC) therapies for patients with MI,

on hospitalisation for HF (HHF), CV death, and other cardiometabolic outcomes via a hierarchical composite endpoint (consists of incidence of non-fatal MI, AF/flutter event, new onset of T2DM, severity of heart failure symptoms assessed using NYHA class, as well as ≥5% weight loss).

Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine whether the clinical benefit of dapagliflozin 10 mg once daily (QD) is superior in relation to placebo when added to SoC in patients without diabetes with myocardial infarction and impaired left ventricular systolic function during the index MI hospitalisation. Clinical benefit is reduced risk of Death, Heart Failure, non-fatal MI, AF/flutter, new onset of T2DM, symptoms of HF as measured by NYHA class, as well as reduced Body weight, in relation to placebo	The hierarchical composite endpoint of: 1. Death (first CV death, followed by non-CV death) 2. Hospitalisation due to heart failure (first adjudicated, followed by investigator reported) 3. Non-fatal MI 4. AF/flutter event 5. New onset of T2DM 6. NYHA class at last visit 7. Body weight decrease of at least 5% at last visit
Secondary	
To determine whether the clinical benefit of dapagliflozin 10 mg once daily (QD) is superior in relation to placebo when added to SoC in patients without diabetes with myocardial infarction and impaired left ventricular systolic function during the index MI hospitalisation. Clinical benefit is reduced risk of Death, Heart Failure, non-fatal MI, AF/flutter, new onset of T2DM and symptoms of HF as measured by NYHA class, in relation to placebo	The hierarchical composite endpoint of: 1. Death (first CV death, followed by non-CV death) 2. Hospitalisation due to heart failure (first adjudicated, followed by investigator reported) 3. Non-fatal MI 4. AF/flutter event 5. New onset of T2DM 6. NYHA class at last visit
To demonstrate the superiority of dapagliflozin 10 mg once daily (QD) versus dapagliflozin 10 mg placebo to match in reducing the incidence of CV death or HHF when added to SoC in non-diabetic patients with myocardial infarction and impaired left ventricular systolic function during the index MI hospitalisation	Time to the first occurrence of any of the components of this composite: • HHF • CV death

Objectives	Endpoints
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing MI, stroke or CV death (MACE) when added to SoC	Time to the first occurrence of any of the components of this composite: • MI • Stroke (incl. ischaemic, haemorrhagic and undetermined stroke) • CV death
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of CV death when added to SoC	Time to CV death
To investigate whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of fatal or non-fatal MI when added to SoC	Time to the first occurrence of a fatal or a non-fatal MI
To determine whether dapagliflozin 10 mg QD, compared with placebo, reduces the incidence of new onset T2DM in MI patients when added to SoC	Time to new onset of T2DM
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing Body Weight when added to SoC	Change from baseline in Body weight
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of hospitalisation for any cause when added to SoC	Time to hospitalisation for any cause
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of all-cause mortality when added to SoC	Time to death of any cause
Tertiary/Exploratory	
CCI	

Objectives	Endpoints
	CCI
CCI	
Safety	
To evaluate the safety of dapagliflozin 10 mg QD in clinically stable patients with ST segment elevation myocardial infarction (ST)- or non-ST elevation myocardial infarction initiated on post-MI therapies and without an established diagnosis of type 1 diabetes mellitus (T1DM) or T2DM	Adverse events defined as events that lead to: • death; or • hospitalisation

For Tertiary/Exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is a multicentre, parallel group, event-driven, registry-based randomised controlled trial (R-RCT), double-blind, placebo-controlled phase 3 study in patients without diabetes

presenting with myocardial infarction (MI) (STEMI or NSTEMI) and impaired regional or global LV systolic function or definite evidence of Q wave MI on ECG. The study is conducted in Sweden and in the United Kingdom (UK) and will randomise about 6400 patients. In the study the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to SoC therapy will be evaluated for the prevention of hospitalisation for HF or CV death. The study will utilise 2 high-quality national, population-based clinical registries: (1) the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (Jernberg et al 2010) and (2) the UK-based Myocardial Ischaemia National Audit Project (Herret et al 2010).

The R-RCT contains a framework, which allows for randomisation and blinding and enables a pragmatic data collection using existing clinical registry data with readily available trial infrastructure facilitating data and endpoint collection. The study design is intended to ensure a robust yet streamlined trial capable of producing high-quality evidence of clinical effectiveness and safety.

In February 2023, to address substantially lower than anticipated observed blinded primary endpoint event rate among recruited patients, the study was modified from an event-driven time-to-event approach to a hierarchical composite endpoint approach. The effect of dapagliflozin 10 mg versus placebo, given once daily in addition to SoC therapy will be evaluated for cardiometabolic outcomes. Accordingly, the sample size was re-calculated and reduced from about 6400 to approximately 4000 patients.

Disclosure Statement

This is a parallel group treatment study with 2 arms that is participant and investigator blinded.

Number of Participants

Patients admitted with MI to Coronary care units will be consecutively screened for participation to achieve at least 6400 randomly assigned to study intervention and 6400 evaluable participants.

Screened [a]	Estimated 6400 participants
Randomly assigned	Estimated 6400 participants
Evaluable participants	Estimated 6400 participants

[a] See Section 5.4 for definition.

In February 2023, the study was modified, and estimated number of screened, randomly assigned, and evaluable participants were re-calculated and reduced from 6400 to approximately 4000 accordingly.

Intervention Groups and Duration

The study will compare treatment with dapagliflozin 10 mg once daily with dapagliflozin 10 mg placebo to match in parallel treatment arms and at a 1:1 randomisation ratio. This study is event driven. The anticipated duration of the study is approximately 30 months with an estimated median treatment period for a patient of 21 months. The study closure procedures will be initiated when the predetermined number of primary endpoints are predicted to have occurred (n = 722) ie, the primary analysis censoring date. The study duration may be changed if the event rate or randomisation rate is different than anticipated. The study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the Data Monitoring Committee review.

In February 2023, the study was modified from an event-driven time-to-event approach to a hierarchical composite endpoint approach. The sample size was re-calculated and reduced from about 6400 to approximately 4000 patients and the median treatment period for a patient of 21 months was changed to a minimum follow-up time of 3 months for each patient.

Data Monitoring Committee: Yes

Statistical Methods

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio of 0.80 between dapagliflozin and placebo, using a 2-sided alpha of 5%, 722 primary endpoint events will provide a statistical power of 85% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo.

The study is event driven. With an annual event rate of 7.5% in the placebo treatment group, 6400 patients are estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 21 months. The sample size, duration of recruitment period, and total study duration may change depending on the recruitment rate and event rate of the primary endpoint.

All patients who have been randomised to study treatment will be included in the Full Analysis Set irrespective of their protocol adherence and continued participation in the study. The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the intention to treat principle using the Full Analysis Set, using events confirmed by adjudication.

In the analysis of the primary composite endpoint, treatments (dapagliflozin versus placebo) will be compared using a Cox proportional hazards model with a factor for treatment group. The p-value, hazard ratio and 95% confidence interval will be reported. An interim analysis is

planned to be performed when 2/3 of the primary endpoints are adjudicated, using a Haybittle-Peto rule. The interim analysis will assess superiority of dapagliflozin to placebo.

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilised. No multiplicity control is placed on the exploratory endpoints.

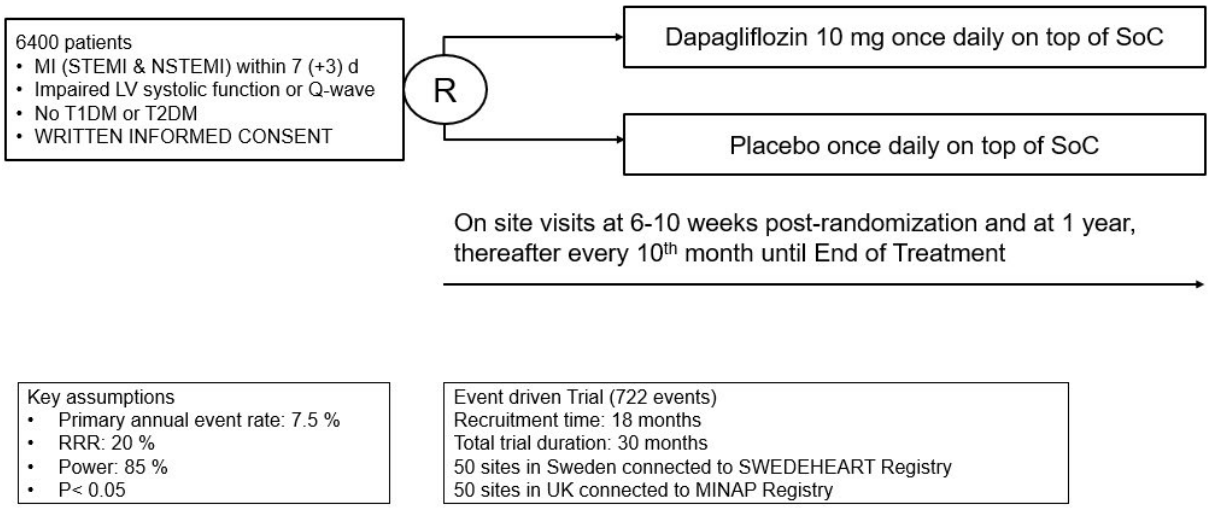
In February 2023, the primary objective of the study was revised to determine if the clinical benefit of dapagliflozin is superior in relation to placebo and this objective will be assessed with a hierarchical composite endpoint and analysed using the win-ratio method. Assuming a true win-ratio of 1.20 between dapagliflozin and placebo, 4000 patients will provide a statistical power of 80% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo.

All patients who have been randomised to study treatment will be included in the Full Analysis Set irrespective of their protocol adherence and continued participation in the study. The primary variable is a hierarchical composite endpoint, consisting of 7 components, assessed in the order of clinical importance, and will be analysed with the win-ratio method.

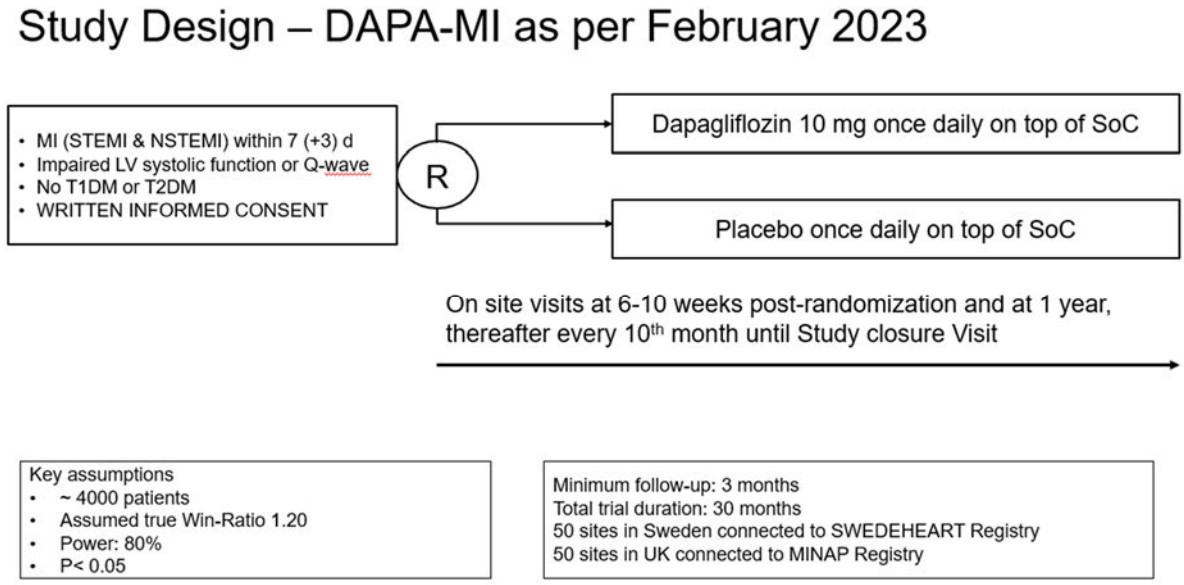
The primary analysis will be based on the intention to treat principle using the Full Analysis Set.

1.2 Schema

Figure 1 Study Design



SoC, Standard of Care, LV, left ventricular; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; R, randomisation; UK, United Kingdom; RRR, Relative Risk Reduction; MINAP, Myocardial Ischaemia National Audit Project; SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies



SoC, Standard of Care, LV, left ventricular; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; R, randomisation; UK, United Kingdom; MINAP, Myocardial Ischaemia National Audit Project; SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure [a]	Screening within 7 days (+3 days) after MI and prior to randomisation	Intervention period				Premature treatment discontinuation visit (PTDV)	Study Closure Visit (SCV)	Details in CSP section or Appendix
		Day 1 (within 7 (+3) days from MI)	Week 8 (±14 days)	Year 1 (±1 month)	Month 22 and onwards (±1 month)			
Visit	**NA**	**1**	**2**	**3**	**4+**			
Visit type		Randomisation	1st routine follow-up	2nd routine follow-up	Study-specific visit (every 10th month until SCV)			
Informed consent	X							Section 5.1
Inclusion and exclusion criteria		X						Sections 5.1 and 5.2
STEMI/NSTEMI (index MI)		X						NA
Reperfusion treatment (index MI)		X						NA
Demography		X						NA
Medical history [b]		X						NA
Relevant risk factors [c]		X	X	X	X	X	X	NA
Systolic and diastolic BP		X	X	X	X	X	X	NA
Weight		X	X	X	X	X	X	NA
Height		X						NA

Table 1 Schedule of Activities

Procedure [a]	Screening within 7 days (+3 days) after MI and prior to randomisation	Intervention period				Premature treatment discontinuation visit (PTDV)	Study Closure Visit (SCV)	Details in CSP section or Appendix
		Day 1 (within 7 (+3) days from MI)	Week 8 (±14 days)	Year 1 (±1 month)	Month 22 and onwards (±1 month)			
Visit	**NA**	**1**	**2**	**3**	**4+**			
NYHA Classification (I-IV)			X	X	X	X	X	NA
CCS angina class (I-IV)			X	X	X	X	X	NA
LVEF assessment [d]		X						NA
Troponin (peak value)		X						Sections 8.1.2, 8.9.2
Serum creatinine for estimated glomerular filtration rate (eGFR)		X						NA
Pregnancy test (β-hCG) [e]		X						NA
HbA1c		X	X	X	X	X	X	Sections 8.1, 8.9
ECG		X	X	X	X	X	X	NA
Efficacy endpoints [f]			X	X	X	X	X	Section 8.1, Appendix A 7,
Safety events [g]		X	X	X	X	X	X	Section 8.3, Appendix B

Table 1 Schedule of Activities

Procedure [a]	Screening within 7 days (+3 days) after MI and prior to randomisation	Intervention period				Premature treatment discontinuation visit (PTDV)	Study Closure Visit (SCV)	Details in CSP section or Appendix
		Day 1 (within 7 (+3) days from MI)	Week 8 (±14 days)	Year 1 (±1 month)	Month 22 and onwards (±1 month)			
Visit	**NA**	**1**	**2**	**3**	**4+**			
Additional revascularisation therapy (PCI/CABG)		X	X	X	X	X	X	NA
ICD implantation			X	X	X	X	X	N/A
EQ-5D-3L (Sweden only) [h]			X	X				Section 8.11
Device deficiencies		X	←==========		==========→	X	X	Section 8.2.4
Concomitant medication [i]		X	←==========		==========→	X	X	Section 6.5
Study intervention dispensed /collected		X [j]	X			X [k]	X [k]	Section 6.1

[a] Procedures conducted as part of the participant's routine clinical management (eg, blood tests, ECG, LVEF) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

[b] Previous MI, Previous stroke, Previous HF, Previous PCI, Previous cardiac surgery, Prehospital CPR, history of Atrial Fibrillation/Atrial flutter.

[c] Smoking, hypertension, dyslipidaemia (defined as statin treatment), From Visit 2 and onwards only smoking and diabetes.

[d] From Visit 2 and onwards only if new LVEF evaluation has been performed in clinical routine.

[e] Women of childbearing potential only.

[f] Efficacy events, any potential heart failure hospitalisation and all fatal events will be sent for adjudication to evaluate if fulfilling criteria for endpoint event. In addition, MI and stroke endpoints as judged by the Investigator will be reported (for Guidance of definitions for MI and Stroke endpoints see Appendix A 7)

[g] Serious adverse events (defined as adverse events that leads to hospitalisation or death), will be collected from randomisation.

[h] Version used in SEPHIA registry. EQ-5D-5L will be collected from Unify App users (in both UK and Sweden).
[i] ASA, Statins, ACE inhibitors/ARB, Antiplatelets other than ASA, Anticoagulants, Beta Blockers, MRA, Oral diabetic treatment, Insulin, Diuretics.
[j] Study Intervention dispensation only.
[k] Study Intervention collection only.

ACE inhibitors, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ASA, acetylsalicyclic acid; BP, blood pressure; β-hCG, Beta human chorionic gonadotropin; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CPR, cardiopulmonary resuscitation; CSP, Clinical Study Protocol; NA, not applicable; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EQ-5D-3L, EuroQol five-dimensional three-level questionnaire; HbA1c, glycated haemoglobin; HF, Heart Failure; ICD, implantable cardioverter defibrillator ; ICF, Informed Consent Form; IRT, Interactive Response Technology; LVEF, Left Ventricular Ejection Fraction; MI, myocardial infarction; MRA, Mineralocorticoid receptor antagonist ; NSTEMI, non-ST segment elevation myocardial infarction; NYHA, New York Heart Association; PCI percutaneous coronary intervention; PTDV, premature treatment discontinuation visit; SCV, study closure visit; SoA. Schedule of Activities; STEMI, ST segment elevation myocardial infarction.

2 INTRODUCTION

An estimated 18 million individuals die from cardiovascular (CV) diseases annually, which accounts for approximately 30% of all global deaths, and places CV disease both as the leading global cause for years of life lost and as the leading cause of total number of deaths (Collaborators 2017). Acute MI is a major contributor to CV morbidity and mortality, globally estimated to occur in 7 million individuals annually (Piepoli et al 2016). The 1-year mortality for MI is estimated at 10%, and the risk for suffering a second major adverse CV event (MACE) among MI survivors is estimated at 20% within 1 year after the event (Piepoli et al 2016).

In parallel with a gradual implementation of new, effective and guideline-supported MI treatments, such as percutaneous coronary intervention (PCI), dual antiplatelet therapy, statins and angiotensin-converting enzyme (ACE) inhibitors, the overall prognosis following MI has substantially improved over time (Szummer et al 2017; Szummer et al 2018; Townsend et al 2015). However, this observed improvement in MI prognosis seems to have reached a plateau during recent years, coinciding with a period where few new breakthrough treatment concepts have been introduced within the MI treatment paradigm (Szummer et al 2017; Szummer et al 2018).

Survivors of MI thus remain at substantial risk for new MACE, CV death (Jernberg et al 2015) and for developing HF (Desta et al 2017). The development of HF following an MI episode is strongly associated with burdensome symptoms, poor functional status and reduced health-related quality of life (Nieminen et al 2015), and portend an unfavourable long term prognosis (Nunez-Gil et al 2010; Steg et al 2004; Wang et al 2016). Heart failure is also one of the leading causes of all hospital admissions, bringing on substantial costs for the health care systems. The current therapeutic strategies available to minimise the risk for development of HF following MI were all introduced more than a decade ago and include early reperfusion therapy, early initiation and proper dose-titration of ACE inhibitors/angiotensin II receptor blockers (ARBs) and aldosterone receptor antagonists, and careful evaluation and re-evaluation of indications for beta-blocker therapy during and after the MI hospitalisation. Despite these advancements, MI patients remain at high CV risk and at high risk for developing HF. Therefore, MI therapies that could prevent the development of HF and reoccurrence of major CV events represent a large and partly unmet medical need.

2.1 Study Rationale

There is an unmet medical need in patients who have suffered a MI. Dapagliflozin treatment (and other sodium glucose co-transporter 2 [SGLT2]) has shown CV health benefits in patients with type 2 diabetes mellitus (T2DM) and either established atherosclerotic CV disease or CV risk factors. Recent confirmatory evidence has shown such benefits also in patients without diabetes with chronic HF and reduced ejection fraction. This study seeks to

determine dapagliflozin's potential in the early prevention of serious complications, hospitalisations for HF or CV death, immediately following a MI.

In February 2023, it was concluded the observed primary endpoint event rate in the DAPA-MI study was substantially lower than anticipated. Therefore, it was decided to revise the primary endpoint to evaluate the effect of dapagliflozin on cardiometabolic outcomes, assessed by a hierarchical composite endpoint and a Win-ratio analysis.

2.2 Background

The development of HF following an acute myocardial ischaemia episode is strongly associated with incapacitating symptoms, poor functional status, reduced health-related quality of life and unfavourable long-term prognosis (Nieminen et al 2015, Nunez-Gil et al 2010). Therefore, MI therapies that could prevent the development of HF as well as reoccurrence of major CV events represent a large and unmet medical need. In large outcome studies, treatment with dapagliflozin have been shown to prevent HF events and CV death in T2DM patients at high risk for, or with established atherosclerotic CV disease (Wiviott et al 2019), and it has also been confirmed that dapagliflozin constitutes an effective treatment option in patients with established HF and reduced ejection fraction (HFrEF) with and without T2DM (McMurray et al 2019).

2.2.1 Dapagliflozin Mode of Action

For a detailed description of the chemistry, pharmacology, efficacy, and safety of dapagliflozin please refer to the Investigator's Brochure (IB).

Dapagliflozin is the first in a class of compounds referred to as SGLT2 inhibitors. SGLT2 is localised to the renal proximal tubule where it reabsorbs about 90% of the ~ 180 g of glucose normally filtered through the glomeruli each day (Sarafidis et al 2019; Zhang and Liu 2016). SGLT2 inhibition therefore leads to pharmacologically controlled glucosuria. Dapagliflozin is a highly potent, selective, and reversible oral SGLT2 inhibitor. A pharmacokinetic half-life of 12.5 hours, due to the C-aryl glucoside-derived chemical structure, allows for the oral administration of dapagliflozin once daily. In patients with diabetes, SGLT2 inhibition reduces renal glucose reabsorption and consequently increases urinary excretion of excess glucose, reduces fasting and postprandial glucose, and reduces circulating glycated haemoglobin (HbA1c). The persistent loss of calories via the urine results in a negative energy balance and in the reduction of total body fat and weight loss. Dapagliflozin also induces diuresis, natriuresis, and decreases blood pressure (BP) without concomitantly trigger an increase in sympathetic tone. Dapagliflozin was originally developed to improve glycaemic control in adult patients with T2DM. Subsequent clinical development programmes have assessed dapagliflozin in the clinical management of type 1 diabetes mellitus (T1DM), and dapagliflozin's cardiorenal benefits in diabetic and non-diabetic subjects, including those with HF and chronic kidney disease (CKD). As of 4 October 2019, more than 20000 subjects have

been treated in clinical trials (CTs) with dapagliflozin for T2DM, more than 1000 subjects for T1DM, and more than 4000 subjects for HF.

2.2.2 Cardiovascular Benefits of Dapagliflozin

Dapagliflozin have been extensively studied in phase IIb and phase III drug development programmes, and has been shown to exert protective cardiorenal effects in patients with diabetes and established atherosclerotic CV disease or CV risk factors, reducing the incidence of hospitalisation for heart failure (HHF) and CV death (Wiviott et al 2019), and attenuating progression to CKD (Mosenzon et al 2019). Furthermore, in a pre-specified subgroup analysis of patients with T2DM and a history of MI included in the DECLARE-TIMI 58 trial, dapagliflozin also reduced the risk of the composite of MI, ischaemic stroke or CV death (hazard ratio (HR) 0.84, 95% confidence interval (CI) 0.72-0.99) (Furtado et al 2019).

In addition to dapagliflozin's positive glycaemic and CV protective health benefits in patients with diabetes, evidence suggests that the observed CV benefits from SGLT2 inhibition in patients with diabetes mellitus is best explained by multifaceted positive actions on pathophysiological factors linked with CV disease, that to a large extent are uncoupled from the blood glucose lowering effect per se. The effects are likely driven by adaptive changes inflicted by the continuous loss of glucose but are catalysed by diabetes-independent factors such as reduced sodium load, circulating blood volume, BP and body weight. This concept is further supported by the observation that the principal CV health benefits from SGLT2 inhibition in the major outcome trials in T2DM conducted hitherto were observed very early during the study courses (ie, before any effect of blood glucose lowering on CV outcomes could be expected). It is therefore highly plausible, that the observed CV benefits of SGLT2 inhibition may extend outside the scope of diabetes mellitus populations, a hypothesis that was recently confirmed in a large outcome trial in patients with HF and reduced ejection fraction, the DAPA-HF trial (McMurray et al 2019). Data from healthy volunteers also shows that by inhibiting SGLT2, dapagliflozin effectively blocks the reabsorption of sodium and glucose in the kidney in healthy subjects, indicating that the drug mechanism works in patients both with and without diabetes.

Although the exact causal mechanisms responsible for the broadly observed CV benefit of dapagliflozin is still incompletely understood, there are several proposed mechanisms of action—uncoupled from the glucose lowering effect— by which SGLT2 inhibitors can act as cardioprotective agents. These includes but are not limited to: (1) a diuretic effect with a preferential effect on interstitial volume congestion (Hallow et al 2018), (2) Positive hemodynamic effects due to improvement in left ventricular loading conditions (ie, reduced preload and afterload) (Lan et al 2019), (3) positive influence on left ventricular remodelling following MI, as demonstrated in non-diabetic animal models (Lahnwong et al 2018, Santos-Gallego et al 2019), (4) increase in haematocrit levels and thus oxygen transporting capacity due to decreased plasma volume and an erythropoietin-induced increase in erythrocyte counts

(Sarafidis et al 2019), (5) mitigation of excess neurohormonal activation and extent of myocardial damage following a MI (Lahnwong et al 2018) and (6) continuous off-target inhibition of sodium-proton antiporters by SGLT2 inhibitors, an action that potentially mimic's ischaemic preconditioning mechanisms that may protect cardiomyocytes during hypoxic conditions (McCullough et al 2018).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of dapagliflozin can be found in the IB.

The expected benefits in the post MI population is based on that SGLT2 inhibition with dapagliflozin is associated with several known or postulated cardioprotective effects. In large outcome studies, treatment with dapagliflozin have been shown to prevent HF events and CV death in T2DM patients at high risk for, or with established atherosclerotic CV disease, and it has also been confirmed that dapagliflozin constitutes an effective treatment option in patients with established HFrEF with and without T2DM. Observations from mechanistic studies have demonstrated multifaceted CV protective effects of dapagliflozin including influence on cardiac loading conditions, energy substrate utilisation and left ventricular remodelling processes ─ which may also be of clinical benefit in the early phase after a MI.

The safety profile for dapagliflozin is very well characterised. The risk profile in the post MI population is expected to be similar to the known safety profile. In the DECLARE-TIMI 58 trial dapagliflozin 10 mg was evaluated generating comprehensive safety data in a high-risk CV risk T2DM population including patients with established CV disease. Regarding post MI patients an analysis was performed of the subgroups of patients in the DECLARE-TIMI 58 trial with prior MI at baseline (n = 3,584) versus no prior MI (n = 13,576). The safety outcomes in the dapagliflozin-treated patients were similar between subgroups (Furtado et al 2019, Wiviott et al 2019). The DAPA-HF study randomised patients with HFrEF (n = 4,744) including both patients without diabetes (≈ 55%) and patients with T2DM at baseline (≈ 45%). The safety and tolerability were generally consistent between patients with T2DM and patients without diabetes (McMurray et al 2019).

2.3.1 Risk Assessment

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
Hypotension	Dapagliflozin causes an osmotic diuresis, which may lead to hypotension. In addition, many drugs introduced post-MI, as per	Inclusion criteria: Patients should be hemodynamically stable at randomisation (no episodes of

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	clinical routines, are affecting blood pressure.	symptomatic hypotension, or arrhythmia with hemodynamic compromise in the last 24 hours).
Study procedures		
Visit schedule/time between visits	Being a pragmatic trial, timing of visits is aligned with routine clinical practice.	In addition to the visits according to clinical routine the first year, patients will be followed up with visits every 10th month until study completion. Patients can contact site personnel as needed also between visits.

MI, Myocardial Infarction; BP, blood pressure

2.3.2 Benefit Assessment

All MI patients in the study will be optimally treated according to Standard of Care (SoC), and dapagliflozin or placebo will be added on top of this treatment. The hypothesis is that dapagliflozin will reduce hospitalisation for HF or CV mortality in patients randomised to active drug. Furthermore, dapagliflozin is also known to decrease body weight (or prevent weight gain) as well as lowering BP and is believed to be nephroprotective through mechanisms uncoupled from the blood glucose lowering effect per se. These effects of dapagliflozin could all potentially be of benefit in the target population that have recently suffered an MI. All patients participating in CTs irrespective of whether treated with active treatment or not, generally receive closer medical attention.

In February 2023, the primary endpoint was revised to assess the potential benefit of dapagliflozin in the target population on HHF, CV death, and other cardiometabolic outcomes.

2.3.3 Overall Benefit: Risk Conclusion

Participation in this study should present a minimal and acceptable risk to patients who meet the inclusion/exclusion (I/E) criteria and consent to take part in the study, with regard to the substantial non-clinical and clinical experience with dapagliflozin, the potential CV benefit that the drug is hypothesised to exert in the target population due to its mechanism of action, and the generally safe and well tolerated character of the drug. The well-tolerated character is also consistent in a T2DM population with established CV disease and prior MI, as well as in a HFrEF population without diabetes.

3 OBJECTIVES AND ENDPOINTS

The table below presents study Objectives and Endpoints.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine whether the clinical benefit of dapagliflozin 10 mg once daily (QD) is superior in relation to placebo when added to SoC in patients without diabetes with myocardial infarction and impaired left ventricular systolic function during the index MI hospitalisation. Clinical benefit is reduced risk of Death, Heart Failure, non-fatal MI, AF/flutter, new onset of T2DM, symptoms of HF as measured by NYHA class, as well as reduced Body weight, in relation to placebo	The hierarchical composite endpoint of: 1. Death (first CV death, followed by non-CV death) 2. Hospitalisation due to heart failure (first adjudicated, followed by investigator reported) 3. Non-fatal MI 4. AF/flutter event 5. New onset of T2DM 6. NYHA class at last visit 7. Body weight decrease of at least 5% at last visit
Secondary	
To determine whether the clinical benefit of dapagliflozin 10 mg once daily (QD) is superior in relation to placebo when added to SoC in patients without diabetes with myocardial infarction and impaired left ventricular systolic function during the index MI hospitalisation. Clinical benefit is reduced risk of Death, Heart Failure, non-fatal MI, AF/flutter, new onset of T2DM and symptoms of HF as measured by NYHA class, in relation to placebo	The hierarchical composite endpoint of: 1. Death (first CV death, followed by non-CV death) 2. Hospitalisation due to heart failure (first adjudicated, followed by investigator reported) 3. Non-fatal MI 4. AF/flutter event 5. New onset of T2DM 6. NYHA class at last visit
To demonstrate the superiority of dapagliflozin 10 mg once daily (QD) versus dapagliflozin 10 mg placebo to match in reducing the incidence of CV death or HHF when added to SoC in non-diabetic patients with myocardial infarction and impaired left ventricular systolic function during the index MI hospitalisation	Time to the first occurrence of any of the components of this composite: • HHF • CV death
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing MI, stroke or CV death (MACE) when added to SoC	Time to the first occurrence of any of the components of this composite: • MI • Stroke (incl. ischaemic, haemorrhagic and undetermined stroke) • CV death

Table 3 Objectives and Endpoints

Objectives	Endpoints
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of CV death when added to SoC	Time to CV death
To investigate whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of fatal or non-fatal MI when added to SoC	Time to the first occurrence of a fatal or a non-fatal MI
To determine whether dapagliflozin 10 mg QD, compared with placebo, reduces the incidence of new onset T2DM in MI patients when added to SoC	Time to new onset of T2DM
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing Body Weight when added to SoC	Change from baseline in Body weight
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of hospitalisation for any cause when added to SoC	Time to hospitalisation for any cause
To determine whether dapagliflozin 10 mg QD is superior to placebo in reducing the incidence of all-cause mortality when added to SoC	Time to death of any cause
Tertiary/Exploratory	
CCI	

Table 3 Objectives and Endpoints

Objectives	Endpoints
CCI	
CCI	
Safety	
To evaluate the safety of dapagliflozin 10 mg QD in clinically stable patients with ST segment elevation myocardial infarction (ST)- or non-ST elevation myocardial infarction initiated on post-MI therapies and without an established diagnosis of type 1 diabetes mellitus (T1DM) or T2DM	Adverse events defined as events that lead to: • death; or • hospitalisation

4 STUDY DESIGN

4.1 Overall Design

This is a multicentre, parallel group, event-driven, registry-based, randomised, double-blind, placebo-controlled phase 3 study in non-diabetic patients presenting with MI (STEMI or

NSTEMI) and impaired regional or global LV systolic function or definite evidence of Q wave MI on ECG. The study is conducted in Sweden and in the UK. The study addresses a clear unmet medical need in patients with MI (post-MI HF development) and will evaluate the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to SoC therapy, for the prevention of hospitalisation for HF or CV death. The innovative trial design uses a registry-based randomised controlled trial (R-RCT) framework (Lauer and D'Agostino 2013; Nyberg and Hedman 2019), a trial concept not previously used in drug development programmes with the intent of regulatory approval. Based on the availability of adequate web-based registries with full coverage of the target population and available infrastructure for the specific trial requirements, the study will be conducted in Sweden and the United Kingdom, and will utilise 2 high-quality national, population-based clinical registries: (1) the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) (Jernberg et al 2010) and (2) the UK-based Myocardial Ischaemia National Audit Project (MINAP) (Herret et al 2010).

This R-RCT adheres to an innovative trial design integrated within 2 national population-based health quality registries and therefore will be conducted in the setting of routine clinical practice. The R-RCT contains a framework, which allows for randomisation and blinding and enables a pragmatic data collection using existing clinical registry data with readily available trial infrastructure facilitating data and endpoint collection. The study design is intended to ensure a robust yet streamlined trial capable of producing high-quality evidence of clinical effectiveness and safety.

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

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

In February 2023, the study was modified from an event-driven time-to-event approach to a hierarchical composite endpoint approach. The effect of dapagliflozin 10 mg versus placebo, given once daily in addition to SoC therapy will be evaluated for the HHF, CV death, and other cardiometabolic outcomes.

4.2 Scientific Rationale for Study Design

This multi-centre trial has been designed as an R-RCT that combines traditional study design elements within a pragmatic trial framework to provide high quality evidence on the potential benefit of dapagliflozin when administered in the early phase after MI. Traditional design elements such as randomisation and double blinding will minimise potential bias while the pragmatic and streamlined trial elements are expected to capture a broad MI population that will increase external validity and generalisability of study results and at the same time limit

study burden on patients and investigators by usage of existing healthcare infrastructure and enabled by continuous clinical quality registries used in routine health care.

4.3 Justification for Dose

The marketed dose (10 mg QD) of dapagliflozin has been demonstrated to be well tolerated and effective both for the treatment of T2DM and chronic HF. From a pharmacokinetic and pharmacodynamic perspective, 10 mg dapagliflozin is appropriate for use in the target population with recent MI at high risk for developing HF, as this dose is expected to near maximally inhibit SGLT2 and thus exert an adaptive bodily response to the treatment that translate to the strongest CV benefit. In most previous double-blind studies of dapagliflozin in T2DM, the 10 mg dose of dapagliflozin was found to be more effective and with comparative safety as the 2.5 mg and 5 mg doses. Furthermore, the use of only 1 dose (ie, 10 mg QD) of dapagliflozin in this study fit well with the pragmatic trial framework, as dispense of different doses of study drug would complicate the drug delivery process.

4.4 End of Study Definition

The end of study is defined as the last visit of the last subject undergoing the study. A subject is considered to have completed the study when he/she has completed his/her event assessment on or after the primary analysis censoring date (PACD).

The executive committee and AstraZeneca (AZ) will monitor the accrual of endpoint events and when appropriate define the PACD at which time at least the pre-defined target number of 722 subjects with adjudicated events for the primary composite endpoint is expected to have occurred. The study sites will be instructed to plan for study closure visits to be performed within approximately 8 weeks after PACD.

In February 2023, it was decided to remove PACD from the study. As a consequence, the definition of the end of study was modified to the last visit of the last subject undergoing the study. A subject is considered to have completed the study when he/she has completed his/her close-out visit.

The executive committee and AstraZeneca (AZ) will monitor the accrual of patients and when appropriate define a certain date at which time the close-out period will start and the study sites should commence with the study closing visits. The close-out period will extend for at least 10 weeks.

4.5 The DAPA-MI Clinical Context

In Sweden, MI patients are discharged from hospital typically after 2 to 4 days. In routine clinical care, all patients are planned for a visit to a specialised secondary prevention nurse 12

weeks after discharge to check symptoms, assess adherence and potential side effects to medications, and perform up-titration of medication doses. If there are issues, the discharging doctor or the doctor with the assigned patient responsibility is consulted. This doctor will typically be responsible for the dedicated secondary prevention visit at 6 to 10 weeks post discharge (SEPHIA (the national registry of secondary prevention) visit 1) as well as the 12 months follow-up visit (SEPHIA visit 2).

In UK practice, there is more heterogeneity between sites in terms of duration of hospital stay and follow-up arrangements. Generally, patients receive follow-up with the cardiac rehabilitation team, and most have a single outpatient clinic follow-up with a clinician or nurse specialist between 4 and 12 weeks, following which they are mostly discharged back to the care of their general practitioner. However, for the purpose of this study visits will be scheduled at 6 to10 weeks post discharge. Some sites have started to implement arrangements for 12 months follow-up.

For any trial-specific issue, the site investigator will always be informed, thereby maintaining the investigator-patient relationship throughout the study period. All study patients will have the opportunity to contact the research nurses who will have direct contact with the site investigators.

4.6 The Trial Registry Collaborators

4.6.1 The SWEDEHEART

4.6.1.1 Scope

The SWEDEHEART was launched December 2009 following a merger between (1) the national registry of acute cardiac care (RIKS-HIA), (2) the Swedish coronary angiography and angioplasty registry, (3) the Swedish heart surgery registry and (4) the national registry of secondary prevention (SEPHIA) (Jernberg et al 2010). The SWEDEHEART registry is financed by the Swedish government and the Swedish Association of Local Authorities and Regions (the public health care provider), and is supported by the Swedish Heart Association, the National Board of Health and Welfare and the Swedish Heart and Lung Foundation. Participating hospitals are not reimbursed by the registry and costs of local data entry are borne by their internal budget. Uppsala Clinical Research Center (UCR) has developed the web services for the registry and is responsible for administration, quality controls, and statistical reports.

4.6.1.2 Data Collection and Quality Assurance Process

The SWEDEHEART includes all patients admitted to cardiac intensive care units with confirmed MI, and all hospitals in Sweden providing care for MI patients participate in the registry collaboration. All patients are informed about their participation in the registry and maintain the right to opt out from participation. The registry is web-based with all data registered online by the caregiver, where after data is transferred in an encrypted format to a

secure central server. The whole process of care is kept together in one master record, also in cases where the patient is transferred between different units and hospitals. The registry system has error checking routines for range and consistency. Variable definitions are easily available for the user when data are entered, and to reach a high degree of completeness, most of the variables are mandatory. Each hospital can monitor site data completeness online, and the accuracy of imputed data elements are regularly subjected to central monitoring/audits.

For patients with MI, information is collected prospectively for more than 100 variables and include patient demographics, admission logistics, risk factors, past medical history, medical treatment prior to admission, electrocardiographic changes, biochemical markers, other clinical features and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses and discharge medications. For MI patients undergoing coronary angiography/angioplasty, approximately 150 additional variables are registered. For patients who have been hospitalised for MI, a follow-up visit is performed after 6 to 10 weeks and again after 12 months. From these visits approximately 75 new variables are added in the SEPHIA sub registry. The registry platform is interlinked with the Swedish National Population Registry, providing monthly automated updates on time of death. For the present study, a selection of variables, harmonised with variables from the MINAP registry, will continuously be extracted from the registry to the electronic case report form (eCRF) system.

4.6.2 The NICOR/MINAP Registry

4.6.2.1 Scope

The National Institute for Cardiovascular Outcomes Research (NICOR) is a quality improvement and research organisation that collects data and produces analysis to enable UK hospitals and healthcare improvement bodies to monitor and improve the quality of care and outcomes of CV patients. NICOR manages 6 national clinical audits in the UK and is a cross-functional partnership of clinicians, IT experts, analysts, academics and data managers. NICOR provides project, technical and analytical support for the clinical audits and registries. One of the 6 registries that is governed by NICOR is the MINAP, a national registry of patients admitted to hospitals in England and Wales with acute coronary syndromes (ACS). The MINAP registry was established in 1998 to provide participating hospitals with a common mechanism for auditing performance against defined standards of ACS care. By mid-2002 all hospitals providing care for ACS in England and Wales were participating in the registry. Registry oversight is provided by a steering group that represents key stakeholders, including professional bodies, patient groups and the national government. The MINAP registry is funded by the Department of Health and receives no commercial funding. The costs of local data entry are borne by the participating hospitals. Scotland does not take part in MINAP, but hospitals in Scotland can participate in the study, being provided access to the MINAP registry to enter data for those patients who have consented to the study.

In February 2023, given the decision to alter the estimated date for the last subject recruited, as well as delays in the administrative and technical processes required, hospitals in Scotland were not provided with access to the MINAP registry.

4.6.2.2 Data Collection and Quality Assurance Process

The MINAP includes all patients admitted with confirmed MI, and all hospitals in England and Wales providing care for MI patients participate in the registry collaboration. A password-protected webservice is used for data entry and data are uploaded to central servers using encrypted transfer protocols. Patients are identified from their unique National Health Service (NHS) number, which is pseudonymized within the database. The MINAP data entry set-up has automated error-checking routines, including range and consistency checks, and the accuracy of imputed data elements are regularly subjected to monitoring/audits. Online data completeness views are readily available for sites participating in the registry. The registry maintains a data dictionary, containing explanatory details for each unique variable entry.

The MINAP dataset comprises over 100 separate fields covering patient demographics, admission method, clinical features and investigations, medical history, drug treatment before admission, details of reperfusion treatment method, drug treatment in hospital, clinical complications, hospital outcome, discharge diagnosis and discharge pharmacotherapy. MINAP does not collect follow-up data but is linked to the Office for National Statistics' registry and uses each patient's unique NHS number to obtain regular mortality updates. All patients maintain the right to opt out from participation. For the present study a selection of variables, harmonised with variables from the SWEDEHEART registry, will continuously be extracted from the registry to the eCRF system.

4.7 The Study-specific R-RCT Framework

The trial will be randomised and double-blind, conducted as an integrated part of normal clinic workflow and is expected to deliver scientifically robust data in accordance with Good Clinical Practice (GCP) and fulfilling the required standards for regulatory compliance.

This R-RCT utilises the platform of already-existing high-quality health registries (described in Sections 4.6.1 and 4.6.2) to randomise and follow study participants during study course (Nyberg and Hedman 2019). Due to structural similarities between registries in terms of technical set-up and variable capture, these 2 registries allow the CT to be driven by a single set of technical solutions, and to provide consistent data from both registries. The DAPA-MI R-RCT is a stand-alone web-application managing trial processes such as patient randomisation. Continuous capture of relevant efficacy and safety endpoints, within the clinical routine platform is performed via data exports from the SWEDEHEART and UK MINAP registries. The DAPA-MI R-RCT application is used for collection of study-specific baseline data (not included in the MINAP or SWEDEHEART registries), for confirmation of patient eligibility, and for randomisation. A Site Screening Log including all patients entered

in the web application can be downloaded. In addition, a Site Subject and Enrolment log can be downloaded by the site personnel listing all randomised patients at their site.

After randomisation an export of baseline variables from the applicable registry into the eCRF system is performed. In Sweden, part of the follow-up data from 6 to 10 weeks and 12 months post MI hospitalisation will also be collected by exporting data from SWEDEHEART into the eCRF system. The UK part of study requires the implementation of study-specific follow-up routines due to lack of a registry-supported clinical routine for follow-up visits in the MINAP registry. The follow-up in the UK will replicate the follow-up routine in Sweden. Data capture from follow-up visits after 12 months will be performed directly in the eCRF in both UK and Sweden. Vital status will be collected by exports from the registries in both countries throughout the study.

4.8 Study Committees

4.8.1 Executive Committee

The Executive Committee (EC) will be responsible for the overall design, including the development of the protocol and any protocol amendments, supervision, interpretation and reporting (presentations at international congresses and publications in peer reviewed journals) of the study. The EC will make recommendations to AZ regarding early stopping or modifications of the study based on the information received from the Data Monitoring Committee (DMC). The EC will be comprised of designated international academic leaders and non-voting members of the Sponsor, and will operate under a separate EC charter.

4.8.2 Clinical Endpoint Committee

An independent, blinded Clinical Endpoint Committee (CEC) will be appointed jointly by the Sponsors and the academic leadership of the study. The CEC will adjudicate the primary endpoint. Investigators will report potential events via eCRFs in real time. Once a potential event has been identified, a complete package of information will be collected with the goal to send to the CEC within 2 weeks of identification. A packet would be considered complete and allow for assessment if all required data are present. The CEC reviewers would set a target to evaluate the complete package within 4 weeks of receipt. Additional details are provided in the CEC charter.

4.8.3 Data Monitoring Committee

An independent DMC will be appointed jointly by the Sponsors and the academic leadership of the study. The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the trial, and for reviewing the overall conduct of the CT. They will review overall safety in the trial. In addition, the DMC will have the responsibility to assess the efficacy data of the interim analysis and decide if stopping guidelines are met. An Independent statistical group will have access to the

individual treatment codes and will be able to merge these with the collected study data and provide to the DMC while the study is ongoing. The DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee. Additional details are provided in the DMC charter.

In February 2023, the efficacy interim analysis was removed.

5 STUDY POPULATION

The target population includes adult male and female patients in Sweden and in the UK, presenting with ST- or non-ST elevation MI (STEMI or NSTEMI). Patients should be clinically stable and initiated on post-MI therapies according to established international and local guidelines at the time of consent and prior to the randomisation, to both satisfy the adequate SoC and the safety of participants. In this stable phase patients can, for prognostic enrichment purposes, be included if they have signs of impaired regional or global LV systolic function on echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI OR definitive evidence on ECG of Q wave MI (defined as presence of Q waves in 2 or more contiguous leads, excluding leads III and aVR, and meeting all of the following criteria: at least 1.5 mm in depth; at least 30 ms in duration; and, if R wave present, more than 25% of the size of the subsequent R wave).

The estimated glomerular filtration rate (eGFR) should be $\geq$ 20 mL/min/1.73 m^2.

Eligible patients should not have an established diagnosis of T1DM or T2DM at time of admission for the index event. The main reason for this is that CV benefit from SGLT2 inhibition in T2DM is already established in previous trials, and it is therefore hard to claim equipoise in a type 2 diabetes post-MI population (Section 7.1). Type 2 diabetic patients can according to the European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) (Cosentino et al 2019) and other guidelines be on SGLT2 inhibitors or expected to become eligible for such therapy during the trial course. Further, a main underlying hypothesis in the study is that the beneficial cardioprotective effects of dapagliflozin appear independent of the glycaemic effects and can therefore be expected in a non-diabetic patient population.

No patients with chronic symptomatic HF *with* a prior HHF within the last year *and* known reduced ejection fraction (LVEF $\leq$ 40%) will be included, as these patients are likely to become eligible for dapagliflozin treatment during the trial course.

The patient population will be recruited while hospitalised for MI in routine specialist care within cardiology departments in the UK and Sweden. Only patients that fulfill inclusion criteria, have no exclusion criteria and provide written informed consent for study

participation will be randomised. Two national, population-based clinical registries SWEDEHEART and the MINAP will constitute the study platform. This register framework will be used for (1) randomisation of patients and (2) for integral parts of the study follow-up routines.

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

Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study to be screened/randomised to a study intervention. Under no circumstances, can there be exceptions to this rule.

In this protocol, "screened" subjects are defined as those who fulfil I/E criteria and sign informed consent. "Randomised" subjects are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly screened subjects refer to Section 5.4.1.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥ 18 at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Confirmed MI, either STEMI or NSTEMI, according to the fourth universal definition of MI (Thygesen et al 2019), within the preceding 7 days, or 10 days if earlier randomisation is not feasible.

3 Evidence of impaired regional or global LV systolic function at any timepoint during current MI-related hospitalisation (established with echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI) OR definitive evidence on ECG of Q wave MI (defined as presence of Q waves in 2 or more contiguous leads, excluding leads III and aVR, and meeting all the following criteria: at least 1.5mm in depth; at least 30 ms in duration; and, if R wave present, more than 25% of the size of the subsequent R wave).

4 Haemodynamically stable at randomisation (no episodes of symptomatic hypotension, or arrhythmia with haemodynamic compromise in the last 24 hours).

Sex

5 Male or female

Informed Consent

6 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

7 Provision of signed and dated, written informed consent prior to any mandatory study specific procedures, sampling, and analyses.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Known T1DM or T2DM at the time for admission. Patients with hyperglycaemia, but without a diagnosis of diabetes mellitus prior to the index event, are eligible at the discretion of the Investigator. Patients who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath should be assessed for ketoacidosis, and if ketoacidosis is confirmed the patient should not be randomised.

2 Chronic symptomatic HF with a prior HHF within the last year and known reduced ejection fraction (LVEF ≤ 40%), documented before the current MI hospitalisation.

3 Severe (eGFR < 20 mL/min/1.73 m^2 by local laboratory), unstable or rapidly progressing renal disease at the time of randomisation.

4 Severe hepatic impairment (Child-Pugh class C) at the time of inclusion into the trial.

5 Active malignancy requiring treatment at the time of screening, except for basal cell- or squamous cell carcinoma of the skin, presumed possible to treat successfully.

6 Any non-CV condition, eg, malignancy, with a life expectancy of less than 2 years based on the investigator´s clinical judgement.

Prior/Concomitant Therapy

7 Currently on treatment, or with an indication for treatment, with a SGLT2-inhibitor.

8 Known intolerance to dapagliflozin.

Prior/Concurrent Clinical Study Experience

9 Participation in another study with a non-approved investigational drug or blinded treatment with a CV or glucose lowering medication.

Other Exclusions

10 Involvement in the planning and/or conduct of the study (applies to AZ staff, UCR staff and/or staff at the study site).

11 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements, or any condition in the opinion of the Investigator that would make participation unsafe or unsuitable.

12 Previous randomisation in the present study.

13 Women of childbearing potential (ie, those who are not chemically or surgically sterilised or postmenopausal):

(a) Who are not willing to use a highly effective method of contraception (described below), OR

(b) Who have a positive pregnancy test, OR

(c) Who are breast-feeding.

Highly effective birth control methods include: sexual abstinence [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product (IMP), and withdrawal are not acceptable methods of contraception], a vasectomised partner, bilateral tubal occlusion. Medically accepted method of contraception that is considered as highly effective ie, combined (estrogen 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, intrauterine hormone-releasing system (IUS). Women of childbearing potential must agree to use one highly effective methods of birth control, as defined above, from screening throughout the study and to within 16 weeks after last dose of study drug, and must have a negative pregnancy test result at Visit 1.

Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months. The age-specific requirements that apply are as follows:

- Women < 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and have follicle-stimulating hormone levels in the postmenopausal range
- Women ≥ 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment

5.3 Lifestyle Considerations

Not applicable.

5.3.1 Meals and Dietary Restrictions

Not applicable.

5.3.2 Caffeine, Alcohol, and Tobacco

Not applicable.

5.3.3 Activity

Not applicable.

5.4 Screening

Screening

"Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

Potential participants are defined as patients who enter the registries due to an MI hospitalisation (and therefore to be considered for trial participation). The registries will be considered as the potential participants log, covering all MI patients that enters the registries.

Individuals who meet the eligibility criteria will be offered to participate in this study.

Those who do not meet the criteria for participation in this study may be considered for trial participation during any future MI events.

Screen Failures

Participants who are screened but are not randomly assigned in the study (do not get randomisation code), are considered "screen failures".

5.4.1 Procedures for Incorrectly Screened or Randomised Participants

Patients who fail to meet the eligibility criteria should not, under any circumstances, be screened or receive study medication. There can be no exceptions to this rule. Patients who are screened, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment and must be withdrawn from the study. Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AZ study physician immediately, and a discussion should occur between the AZ study physician and the investigator regarding whether to continue or discontinue the patient from treatment. Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. In those cases where

continuation of study therapy is judged not to present a concern related to safety and disease management, the therapy should be continued. The rationale for continuing or stopping study therapy must be clearly documented in medical records by the Investigator. Regardless of what is decided about IP, all randomised patients should remain in the study and the patients should continue to be followed up in accordance with defined study procedures.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Study intervention in this study refers to dapagliflozin 10 mg or matching placebo.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 4 Investigational Products

ARM name	Treatment 1	Treatment 2
Intervention name:	Dapagliflozin 10 mg	Placebo to match
Type	Drug	Drug
Dose Formulation:	Green, plain, diamond shaped, film coated tablets 10 mg	Green, plain, diamond shaped, film coated tablets
Unit Dose Strength	10 mg	placebo
Dose Level:	10 mg once daily	once daily
Route of administration	Per oral	Per oral
Use	experimental	placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and labelling	Study treatment will be provided in bottles. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Study treatment will be provided in bottles. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.
Provider	AstraZeneca	AstraZeneca

IMP, investigational medicinal product; NIMP, non-investigational medicinal product; GMP, Good Manufacturing Practice.

6.1.2 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage of Interventions

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

Only randomised subjects in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The investigator will retain the returned medication until the AZ representative or delegate collects it, along with any medication not dispensed. The AZ representative or delegate will advise on the appropriate method for destruction of unused study medication.

Study medication will be dispensed to patients in AZ standard bottles according to the normal packing procedure for CT material. Delegated study personnel at the sites will exchange the AZ standard caps to CleverCap Lite^{TM} caps for the patient when the study treatment is first dispensed. During this process, the original aluminium lining (seal) welded to the bottle during the packing step at AZ will remain intact and the tablets will therefore remain protected until the patient breaks the lining and takes the first tablet. The change of cap will have no impact on the stability and quality of the tablets.

When the new study medication will be dispensed, the original CleverCap Lite^{TM} will be transferred to the new bottle by the site personnel.

Study drug may be delivered to the patient's home if the patient cannot travel to the site due to the COVID-19 pandemic. In this instance, the patient will be provided with instruction on how to replace the standard cap with CleverCap Lite^{TM} on the new bottle.

Detailed procedure of the cap replacement and documentation will be described in the Site Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All subjects will be centrally assigned to the study treatment using a computerised randomisation functionality webservice supported by the generic R-RCT framework. This computerised randomisation procedure will ascertain allocation concealment and will assign the participants 1:1 to dapagliflozin or matching placebo, and the treatment allocation

generated within the R-RCT framework will be automatically and blindly communicated to an interactive response technology (IRT) at the Sponsor that in turn will govern the dispense of study drug.

The randomisation will be stratified by country (Sweden and UK).

The study will be blinded to both patients and Investigators/site staff. The IRT will provide to the Investigator(s) the kit identification number to be allocated to the patient at the dispensing visit. Study intervention will be dispensed at the study visits summarised in the Schedule of Activities (SoA). Routines for this will be described in the IRT user manual that will be provided to each centre.

The IRT will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit.

Routines for this will be described in the IRT user manual that will be provided to each centre.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AZ, without revealing the treatment given to participant to the AZ staff.

AZ retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.3.1 Emergency Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AZ, without revealing the treatment given to participant to the AZ staff.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment allocation. Individual treatment codes, indicating the treatment allocation for each randomised patient, will be available to the Investigator(s) from the IRT. Routines for unblinding will be described in the

IRT user manual that will be provided to each centre. If the web-based IRT system is not working, unblinding remains possible via a telephone support helpdesk provided by the IRT vendor, available 24 hours per day, 365 days per year. The telephone number for this helpdesk is found in the IRT user manual and on the Patient Card which should be kept by the patient.

The number of individuals at the study site who become aware of the treatment status should be kept to an absolute minimum, including keeping the patient blinded if possible. Treatment with IP should be continued, or re-initiated if interrupted, if considered appropriate.

6.4 Study Intervention Compliance

Treatment compliance will be regularly assessed by the AZ study team and will use "smart pill bottle" technology. The study treatment bottles containing dapagliflozin or matching placebo will be fitted with the CleverCap Lite™ technology, a system that can provide the date and time of every bottle access. Data on treatment compliance from the CleverCap Lite™ system will be wirelessly (using the 3G network) pushed to a central reporting/analytics portal in encrypted format and supervised by the AZ study team. The analytics portal provides individual participant data on exceptions and potential violations from scheduled study treatment dosing. Unexpected dose interruption and/or multiple bottle accesses during the same day will trigger appropriate action from the AZ study team. Detailed process will be described in the Monitoring Plan. Data from the CleverCap Lite™ system on the confirmed treatment protocol violation (time for and duration of the dose interruption) will be documented as described in the Monitoring Plan.

6.5 Concomitant Therapy

All patients should be treated according to regional standards of care for MI. Beyond provision of emergency MI care and appropriate reperfusion strategies, this also includes advice on lifestyle interventions aimed at smoking cessation, optimal BP control, diet and weight control, and increased physical activity. In addition, pharmacological mitigation of associated CV risk factors (eg, BP, lipid-lowering therapies and antithrombotic treatment(s)) represents key risk-reducing measures that should be offered to all patients. Further specific guideline-recommended pharmacologic MI therapies (beta blockers, renin-angiotensin system blockers and mineralocorticoid antagonists) should, in the absence of contraindications for their use, be initiated and properly dos-titrated in eligible patients according to the ESC guidelines for STEMI and NSTEMI patients, respectively (Ibanez et al 2018; Roffi at al 2016).The Sponsor will provide an optional study-specific smartphone application to all participants in an effort to educate patients about MI and recommended lifestyle changes (refer to Section 8.11 for details about the study-supporting smartphone application). Background medications will not be provided by the Sponsor.

6.5.1 Prohibited Medication

Concomitant treatment (ie, treatment in combination with study drug) with open label SGLT2 inhibitors eg, dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and fix dose combinations containing these drugs is prohibited. Also, in situations when the patient is not on IP, treatment with open label SGLT2 inhibitors during the study could interfere with the interpretation of study results and should therefore not be given unless all other possibilities to treat the patient properly has been considered.

6.5.2 Background Medication

The patient should receive SoC therapies indicated in the early and subsequent phase after MI as judged by the Investigator and consistent with international and local guidelines. Standard evidence-based treatments to be considered include (1) antithrombotic treatment (aspirin, P2Y12 inhibitors and/or rivaroxaban in guideline-recommended combinations and treatment durations, including individual bleeding risks in decision-making), (2) BP management and cardioprotective agents (beta-blockers, ACE inhibitors / ARBs, mineralocorticoid/aldosterone receptor antagonists, as guided by BP levels and LV function during the MI hospitalisation) and (3) lipid management (statins, ezetimide, bile acid sequestrants, fibrates, omega 3 fatty acids and PCSK-9 inhibitors, as indicated to meet clinically established treatment goals in terms of S-LDL and S-TG reduction). In MI patients with concomitant non-valvular atrial fibrillation, oral anticoagulation should be maintained (or added) to antiplatelet(s) according to initial MI management strategy (invasive/conservative) and presumed bleeding risk, at the discretion of the Investigator. A proton pump inhibitor should also be considered in all MI patients with a higher than average presumed gastrointestinal bleeding risk.

6.5.3 Other Concomitant Treatment

Medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator.

6.5.4 Recording of Concomitant CV and Glucose Lowering Medications

Adherence to relevant CV medications (eg, antithrombotic, lipid-lowering, and antihypertensive/cardioprotective agents) will be recorded throughout the study, using the routine clinical registry medication data capture. The same workflow will be used to record any initiation of diabetes treatment (peroral glucose lowering agent or insulin). In addition, all concomitant medications will be recorded at the time of any reportable adverse events (AEs).

6.5.5 Invasive Cardiac Procedures

Additional clinically driven invasive cardiac procedures (PCI/coronary artery bypass grafting [CABG]) will be captured within the established registry workflow or recorded in the eCRF system.

6.6 Intervention After the End of the Study

Post-study treatment will not be provided by the Sponsor.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

Subjects may be discontinued from Study Intervention in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe non-compliance with the Clinical Study Protocol
- If a patient develops T2DM during the trial, the decision whether or not to discontinue the investigational treatment rests with the Investigator. The protocol allows that a patient that develops T2DM during the trial is started on other glucose lowering medications than SGLT2 inhibitors. If the Investigator decides that an SGLT2 inhibitor is the only option to treat the patient properly, then the investigational product should be discontinued.
- Diabetic ketoacidosis (DKA): Consider temporarily interrupting IP if DKA is suspected. If DKA is confirmed, IP should be discontinued permanently.
- If a patient develops type 1 diabetes during the trial, the investigational treatment should be permanently discontinued
- If a patient becomes pregnant during the study, the investigational treatment should be discontinued immediately, and an AZ representative should be contacted
- If a patient during the trial is enrolled in another clinical study with non-approved investigational drug administered

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

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

modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.1 Temporary Discontinuation

Temporary interruption of IP may be considered in patients thought to be at substantial risk of volume depletion/hypotension, such as:

1 patients with an acute medical illness potentially causing volume depletion because of inadequate fluid intake or fluid/blood loss (eg, gastroenteritis, gastrointestinal haemorrhage), or
2 patients undergoing major surgery.

During such circumstances, the IP should be re-initiated as soon as the reason for the temporary discontinuation decision is concluded. Temporary discontinuation will be monitored via CleverCap Lite™ portal.

7.1.2 Rechallenge

Patients who have temporarily discontinued IP can resume treatment as soon as, in the opinion of the Investigator, the patient's condition is stable and the patient wishes to resume. No minimum time period is necessary before treatment can resume. Whenever possible, restart of randomised study medication should be encouraged, even if a premature treatment discontinuation visit (PTDV) was previously completed.

7.1.3 Procedures for Permanent Discontinuation of Study Treatment

The investigator should instruct the subject to contact the site before or at the time of stopping study treatment. The preferred follow-up approach for all patients who prematurely and permanently discontinue IP is that the patient undergoes the PTDV and then continues study visits according to plan (refer to Table 1). The PTDV should be done as soon as possible after last IP dose.

The date of last intake of Study treatment should be documented in the eCRF. All Study treatment should be returned by the subject at their next on-site study visit or unscheduled visit.

7.1.4 Evaluation of Volume Status

Hypotension/Volume Depletion

Patients with clinically relevant symptoms/signs of suspected volume depletion and/or hypotension, should have their regular medication reviewed, and consideration given to reducing the dose of, or stopping concomitant non-essential medications, as assessed on an individual basis, including diuretics and drugs that lower BP (except essential treatments – see

below). The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated considering the patient's symptoms and signs. Hypotension may also occur with other BP lowering drugs and once again the need for (and dose of) non-essential agents of this type (eg, calcium channel blockers, alpha adrenoceptor antagonists and nitrates) should also be reconsidered.

Essential Treatments

Essential disease modifying/evidence-based treatments such as beta blockers, angiotensin converting enzyme (ACE) inhibitor or ARBs and mineralocorticoid receptor antagonists, should NOT be reduced in dose or discontinued unless all other measures fail to improve the patient's situation. In acute situations it may be acceptable to interrupt treatment on a temporary basis in certain circumstances (eg, an ACE inhibitor/ARB if the patient has experienced a significant deterioration in renal function, a betablocker if the patient is unduly bradycardic or hypotensive, a mineralcorticoid receptor antagonistMRA if the patient has hyperkalaemia).

Unexpected Acute Declines in Renal Function

Dapagliflozin is a SGLT2 inhibitor, which by its mechanism of action reduces the reabsorption of glucose and sodium in the proximal tubules in the kidney. SGLT2 inhibition has a mild diuretic effect and an initial haemodynamic change with an initial increase in creatinine may occur and should NOT normally result in IP interruption or discontinuation.

If an unexpected, acute decline in kidney function is observed, the patient should be evaluated. Volume depletion, hypotension, inter-current medical problems and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered (the latter especially in men). Several drugs may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be reconsidered.

7.1.5 Ketoacidosis in patients with type 2 diabetes mellitus

There have been reports of ketoacidosis, including diabetic ketoacidosis (DKA), in patients with type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors in previous studies. Patients with type 2 diabetes mellitus on investigational treatment who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of the investigational treatment should be considered and the patient should be promptly evaluated.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, a PTDV visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. AEs as defined in the trial (AEs leading to hospitalisation) will be reported. The Investigator will follow up subjects as medically indicated.

7.3 Lost to Follow up

A participant will be considered potentially lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The term lost to follow-up will be limited to only patients with unknown vital status at study end (if not dead, patients need to have a date last known alive on or after the PACD).

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed potentially lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, repeated telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Efforts to reach the subject should continue until the end of the study. If these efforts to re-establish contact with the subject prove unsuccessful, additional allowed approaches for recovering vital status is by using the available interlinkage procedures with the different national registry sources (as outlined in Sections 4.2.1 and 4.2.2).
- Suggested language, when follow-up status of participant is critical to study outcomes: Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

In February 2023, it was decided to remove PACD from the study. As a consequence, the definition of lost to follow-up was updated and limited to only patients with unknown vital status at the study end (patients not confirmed as either dead or alive at their individual closing visit).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. All screened patients will be entered in the randomisation application and captured in the screening log within the application. See description of the screening log in Section 4.7.
- Procedures conducted as part of the participant's routine clinical management (eg, blood tests, ECG, LVEF) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

Potential endpoint events will be identified (1) when questioning the patient about his/her overall health and symptoms and (2) through information received through standard medical practice (including findings on physical examination, medical imaging, and laboratory data).

Investigators will be encouraged to have a low threshold to submit any potential/possible event that might represent an endpoint. If the event is subject to adjudication, relevant source documents will be assembled. The source documents and relevant eCRF data will then be sent for central adjudication. Detailed instructions regarding endpoint reporting will be provided to the study sites. Additional details about the evaluations of potential endpoint events will be described in the clinical event adjudication charter.

8.1.1 Primary Outcome Assessments

The following potential endpoints should be reported, and source documents submitted for central adjudication:

- All potential HHF events
- All deaths

8.1.1.1 Hospitalisation for Heart Failure

All potential HHF endpoint should be recorded in the eCRF and submitted to the CEC for adjudication. The CEC will adjudicate the events as specified in the CEC Charter.

8.1.1.2 Classification of Death

The CEC members will adjudicate and classify all deaths based on definitions described in the CEC charter. For the purpose of the efficacy analysis, deaths will be subclassified by CV, non-CV and undetermined cause of death.

8.1.2 Secondary Outcome Assessments

1 The secondary endpoints of MI and stroke, constituting either a stand-alone secondary endpoint or part of composite endpoint will rely on investigator reporting and will not be subject to central adjudication. The rationale for this is that diagnoses of MI and stroke are well-defined in broadly accepted guidelines and defined by objective routine diagnosis procedures (ECG and cardiac troponin levels to diagnose MI; and brain imaging to support stroke diagnosis, for guidance see Appendix A 7).

   (a) Fatal or non-fatal MI

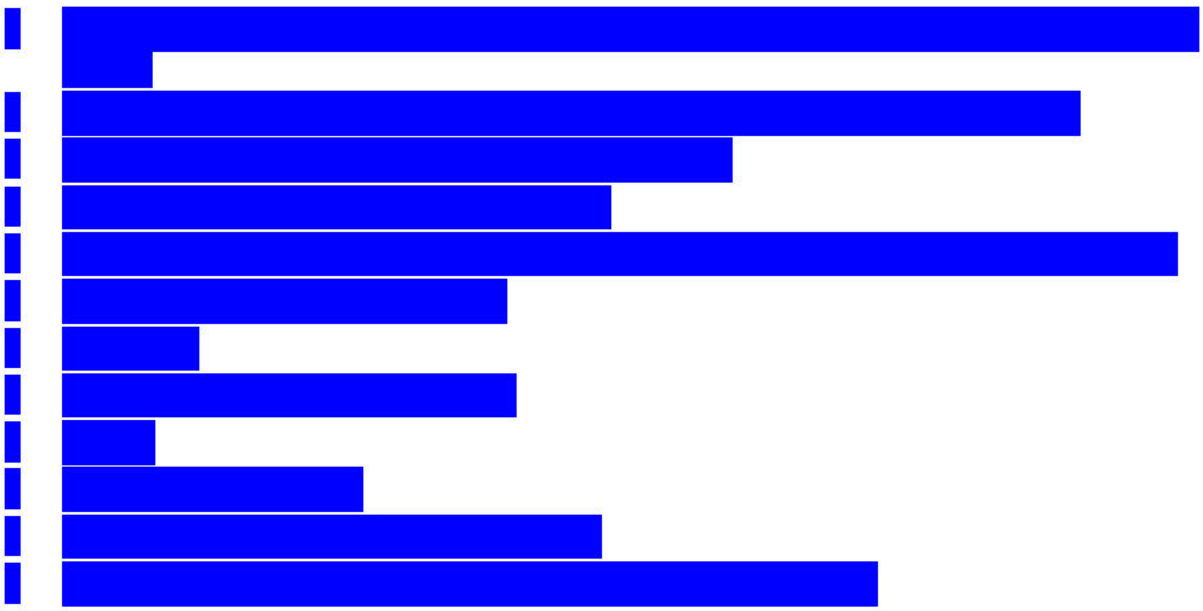
   (b) Stroke (including ischaemic, haemorrhagic, and undetermined stroke)

2 For the secondary endpoint exploring whether dapagliflozin 10 mg QD, compared with placebo, reduces the incidence of new onset T2DM in MI patients when added to SoC, this will rely on investigator reporting and is defined as: 1) reporting of new onset type 2 diabetes mellitus (T2DM) necessitating initiation of treatment with glucose lowering agent OR 2) HbA1c $\geq$ 6.5% (48 mmol/mol) measured by local laboratory at 2 consecutive time points.

For each potential endpoint event, the investigator or delegate will record information in the eCRF.

8.1.3 Exploratory/Tertiary Outcome Assessments

CCI



In February 2023, the primary outcome assessment was revised to be the 7 components of the hierarchical composite endpoint used to evaluate the primary objective of the study. The 7 components ordered in clinical importance are: death, HHF events, non-fatal MI, atrial fibrillation/flutter events, new onset of T2DM, NYHA class at last visit, and body weight loss of at least 5% at last visit.

The key secondary outcome assessment is the same as for the primary outcome, excluding the body weight change component.

The composite endpoint of HHF or CV death will be a secondary composite endpoint.

The secondary endpoint exploring the incidence of hospitalization for any cause was added. This will rely on investigator reporting in SERAE CRF form.

The secondary endpoint of change from baseline to last visit in body weight was added.

The definition of new onset of T2DM was changed to rely on investigator reporting in the dedicated CRF form DMDIAG.

For more details see SAP.

8.2 Safety Assessments

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

Investigators will record data on AEs leading to hospitalisation or death at the scheduled study visits and study closure visit. Data collection for fatal events will be performed also through registry checks. Deaths in both Sweden and the UK are routinely captured by their respective population registries and automatically added to SWEDEHEART and requested for linkage with the MINAP data.

All participating patients will be treated according to regional standards of care for MI and according to clinical routines at the participating study sites. During the course of the study all patients, at all participating sites, will have the opportunity to have direct contact with study nurses dedicated to this study.

8.2.1 Blood Pressure

Blood pressure will be assessed in accordance with normal clinical routines at time points specified in the SoA (Table 1).

8.2.2 Clinical Safety Laboratory Assessments

No clinical safety laboratory tests will be performed within the study. However, assessment of laboratory tests, including serum creatinine, according to clinical practise is recommended.

For information on how AEs based on laboratory tests should be recorded and reported, refer to Section 8.3.5.

8.2.3 Other Safety Assessments

8.2.3.1 Body Mass Index

BMI will be calculated from height and weight at the time points specified in the SoA (Table 1).

8.2.4 CleverCap Lite™ - Device deficiencies

In this study any deficiency observed with the CleverCap™ Lite device will be collected and reported to the manufacturer.

A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

The manufacturers complaint report will be used to collect the deficiency.

8.3 Adverse Events and Serious Adverse Events

In this study only AEs leading to hospitalisation or death will be collected.

With regard to the primary efficacy events of HHF and CV death, all deaths and all potential HF hospitalisation events will be centrally adjudicated, as indicated in Section 8.1. If events of HHF are negatively adjudicated, they will be re-routed as AEs. For the other efficacy endpoints, the investigators will assess if the events are to be reported as endpoint events or re-routed as AEs.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE leading to hospitalisation or death. For information on how to follow/up AEs see Section 8.3.2.

In February 2023, it was decided that the composite of HHF or CV death will no longer be the primary endpoint of the study. No other change to this section.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Reportable AEs will be collected from the time of randomisation, throughout the treatment period and including the follow-up period until the study closure visit.

All reportable AEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 8.3.9. The investigator will submit any updated AE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek reportable AEs in former study subjects. However, if the investigator learns of any AE leading to hospitalisation or death, at any time after a subject’s last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of reportable AEs and the procedures for completing and transmitting SAE reports are provided in Appendix B 3.

8.3.2 Follow-up of Reportable AEs

After the initial SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All reportable AEs will be followed until resolution, stabilisation, the event is otherwise explained, or the subject is lost to follow-up.

Any reportable AEs that are unresolved at the study closure visit are followed up by the Investigator for as long as medically indicated, but without further recording in the case report form (CRF). AZ retains the right to request additional information for any subject with ongoing SAE(s) at the end of the study, if judged necessary.

Reportable adverse event variables

The following variables will be collected for each reportable AE ie, AEs leading to hospitalisation or death:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- Outcome
- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to hospitalisation or death
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'
- Description of AE

8.3.3 Causality Collection

The investigator should assess causal relationship between Investigational Product and each reportable AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’.

Causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs leading to hospitalisation spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', 'Have you been hospitalised due to any of these health problems?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated examinations should only be reported as AEs if they fulfil any criteria for AEs reporting according to this protocol.

If deterioration in an examination is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s) if leading to hospitalisation or death.

Deterioration in an examination which is unequivocally due to disease progression, should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE if fulfilling hospitalisation criterion unless unequivocally related to the disease under study (Sections 8.3.8).

8.3.6 Hy's Law

Not applicable.

8.3.7 Disease Progression

Not applicable.

8.3.8 Disease-Under study

Events of adjudicated hospitalisation for HF, non-fatal or fatal MI, non-fatal or fatal stroke and all-cause mortality will be defined as endpoint events. These events will not be reported to health authorities as SAEs as they are considered part of the natural history of the disease under study.

8.3.9 Reporting of Serious Adverse Events

All AEs leading to hospitalisation or death have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s) and will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AZ representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AZ representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate a reportable AE in the eCRF system, an automated email alert is sent to the designated AZ representative.

If the eCRF system is not available, then the investigator or other study site staff reports a SAE to the appropriate AZ representative by telephone.

The AZ representative will advise the investigator/study site staff how to proceed.

Investigators or other site personnel send relevant eCRF modules by fax to the designated AZ representative.

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

The reference document for definition of expectedness/listedness is the IB for the AZ drug.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AZ except for:

- If the pregnancy is discovered before the study subject has received any study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

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

8.3.10.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AZ representatives within 1day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (Section 8.3.9) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

In the CRF the PREGREP module is used to report the pregnancy. The PREGOUT is used to report the outcome of the pregnancy.

8.3.10.2 Paternal Exposure

Not applicable.

8.3.11 Medication Error

Medication errors with AZ IP are collected in all studies where medication error is possible. Refer to the project specific safety requirements (PSSR) or other appropriate project document for specific considerations for collection of medication errors.

For guidance, refer to AZ Standard Operating Procedure 'Reporting of Individual Safety Events in Clinical Studies.'

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AZ representatives within one day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AZ representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (hospitalisations initial and follow up) calendar days if there is a reportable AE associated with the medication error (Section 8.3.9)

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

8.3.12 Medical Device Deficiencies

Not applicable.

8.4 Overdose

An overdose with associated AEs is recorded if the AE leads to hospitalisation or death and the AE diagnosis/symptoms will be reported on the relevant AE modules in the CRF.

Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single-dose testing in healthy volunteers and up to 100 mg/day in repeat-dose testing for 14 days in healthy volunteers and patients with T2DM. If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

If an overdose on an AZ study drug results in an AE leading to hospitalisation or death then the Investigator or other site personnel inform appropriate AZ representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site.

For overdoses associated with AEs leading to hospitalisation or death, the standard reporting timelines apply, refer to Section 8.3.9.

8.5 Human Biological Samples

Not applicable.

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

Not applicable.

8.5.3 Pharmacodynamics

Not applicable.

8.6 Human Biological Sample Biomarkers

Biomarkers are not evaluated in this study.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation parameters are not evaluated in this study.

8.9 Study Plan and Timing of Procedures

8.9.1 Prerequisites

The listed study-specific measures outlined below assumes:

1 That all study participants are carefully followed according to the routine SWEDEHEART and MINAP hospitalisation and follow-up protocols.

2 That all sites that participates in the study are compliant with the SWEDEHEART and MINAP routines, and that all variables are accurately collected by sites throughout the study.

3 For the post-MI follow-up in the UK, the SEPHIA follow-up routines and variables content will be replicated but will be captured by direct entries on eCRF pages in the eCRF system.

4 That all participating centres maintain a dedicated screening log,

8.9.2 Visit 1: Screening and Randomisation (Day 1)

- The RIKS-HIA/MINAP variables are recorded according to clinical routine including local blood samples as dictated by the registry, of which the following samples are mandatory for study purpose:
  - Troponin (peak value)
  - HbA1c
  - S-creatinine (to be used to calculate eGFR; at local laboratory)
- Patient signs the ICF before any study-specific procedures.
- In women with childbearing potential, a negative pregnancy test needs to be confirmed prior to screening.

- The investigator will assess the inclusion and exclusion criteria.
- LVEF assessment (if part of routine care)
- Index MI characteristics: ECG (STEMI/NSTEMI), any reperfusion treatment
- Required demographic data
- Height and weight
- Systolic and diastolic BP
- Relevant Medical history
- Relevant Risk factors
- Relevant CV and glucose lowering medication
- Any potential efficacy endpoint or safety event will be recorded.
- The patient will be consented, assigned an E-code and randomised in the R-RCT data module, where after the E-code and randomisation number along with date of birth will be pushed to the IRT system that in turn will allocate the randomised treatment.
- IP will be dispensed via IRT to the patient, including assigning the Clever Cap Lite™ for each patient on the first pill bottle. The patient will be instructed to take the IP in accordance with protocol without interruptions and to bring all dispensed bottles and the CleverCap Lite™ to all study visits, and to report any device deficiencies with the CleverCap Lite™. The first IP dose is intended to be taken on the randomization day.

8.9.3 Visit 2: Early Follow-visit, Week 8 (±14 days)

- The investigator or delegate will record all SEPHIA variables, including local blood samples as dictated by the registry. In the UK, variables and local lab samples identical to the SEPHIA process will be captured by Investigators as direct entries in the eCRF.
- ECG
- Systolic and diastolic BP
- Weight
- Relevant Risk factors
- NYHA Classification and CCS angina class
- EuroQol five-dimensional three-level questionnaire (EQ-5D-3L) (in Sweden only)
- HbA1c local lab sample is mandatory for study purposes.
- Relevant CV and glucose lowering medication
- Any potential efficacy endpoint or safety event will be recorded.
- Any revascularisation therapy (PCI/CABG) or ICD implantation
- New IP will be dispensed via IRT to the patient. The patient will be reminded to take the IP in accordance with protocol and without interruptions, and to report any device deficiencies with the CleverCap Lite™.

8.9.4 Visit 3: The Second Follow-up Visit, Year 1 (±1 month)

- The investigator or delegate will record all SEPHIA variables, including local blood samples as dictated by the registry. In the UK, variables and local lab samples identical to the SEPHIA process will be captured by Investigators as direct entries in the eCRF.
- ECG
- Systolic and diastolic BP
- Relevant Risk factors
- Weight
- NYHA Classification and CCS angina class
- EQ-5D-3L (in Sweden only)
- HbA1c local lab sample is mandatory for study purposes.
- Relevant CV and glucose lowering medication
- Any potential efficacy endpoint or safety event will be recorded
- Any revascularisation therapy (PCI/CABG) or ICD implantation
- New IP will be dispensed via IRT to the patient. The patient will be reminded to take the IP in accordance with protocol and without interruptions, and to report any device deficiencies with the CleverCap Lite™.

8.9.5 Visit 4, 5, 6 etc: Study-specific Visit(s), Month 22 (±1 month) and Thereafter Occurring Every 10th Month Until Study Closure Visit

- At this visit, variables and local lab samples identical to the SEPHIA follow-up visit process during the first-year post-randomisation will be captured by Investigators, but as direct entries in the eCRF.
- HbA1c local lab sample is mandatory for study purposes.
- NYHA Classification and CCS angina class
- ECG
- Systolic and diastolic BP
- Weight
- Relevant Risk factors
- Weight
- Relevant CV and glucose lowering medication
- Any potential efficacy endpoint or safety event will be recorded.
- Any revascularisation therapy (PCI/CABG) or ICD implantation
- New IP will be dispensed via IRT to the patient.
- The patient will be reminded to take the IP in accordance with protocol and without interruptions, and to report any device deficiencies with the CleverCap Lite™.

8.9.6 Premature Treatment Discontinuation Visit

Patients who prematurely and permanently discontinue treatment with study medication should return for a PTDV, which will be done as soon as possible after last IP dose (refer to Section 7.1.3).

- At this visit, variables and local lab samples identical to the SEPHIA follow-up visit process will be captured by Investigators, but as direct entries in the eCRF.
- HbA1c local lab sample is mandatory for study purposes.
- NYHA Classification and CCS angina class
- ECG
- Systolic and diastolic BP
- Relevant Risk factors
- Weight
- Relevant CV and anti-hyperglycaemic medication
- Any potential efficacy endpoint or safety event will be recorded.
- Any revascularisation therapy (PCI/CABG) or ICD implantation
- The patient will return remaining IP and report any device deficiencies with the CleverCap Lite™.
- After stopping IP the investigator should ensure that the patient is treated according to standard clinical practice and ascertain there is a proper medical follow-up plan in place.

8.9.7 Study Closure Visit

- At this visit, variables and local lab samples identical to the SEPHIA follow-up visit process will be captured by Investigators, but as direct entries in the eCRF.
- HbA1c local lab sample is mandatory for study purposes.
- ECG
- Systolic and diastolic BP
- Relevant Risk factors
- NYHA Classification and CCS angina class
- Weight
- Relevant CV and glucose lowering medication
- Any potential efficacy endpoint or safety event will be recorded.
- Any revascularisation therapy (PCI/CABG) or ICD implantation
- The patient will return remaining IP and report any device deficiencies with the CleverCap Lite™.
- After stopping IP, the investigator should ensure that the patient is treated according to standard clinical practice and ascertain there is a proper medical follow-up plan in place.

8.9.8 Unscheduled Visits

An unscheduled visit may occur in-between scheduled visits eg, to follow up on potential endpoint or safety events.

8.10 Clinical Trial Data Model

The investigator will ensure that data are accurately recorded in the registries (SWEDEHEART/MINAP) for all subjects at every scheduled contact and according to the established variable definitions in the registries. The investigator will also ensure that any additional study-specific data is accurately recorded in on eCRFs. Data collected from both the web-based registry services and from eCRFs will be managed by an Electronic Data Capture System that will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, and timelines of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue Study treatment.

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

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. At site level a specific log to record details of all potential participants will be kept to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of the ICF (eg, evaluation of LVEF during the current hospitalisation) may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.11 Unify™ Mobile Software Application

The Unify™ mobile software application, and associated website system, will provide digital support to patients from screening through to, and including, follow-up. The system will provide patients and site study staff with information and tools relevant to the conduct of the study in accordance with this protocol. This will comprise treatment medication reminders, clinical visit reminders, primary endpoint reporting functionality, educational content relating to the disease and medication, and ability to collect EQ-5D-5L data.

MI patients will be asked to complete the EQ-5D-5L quality of life questionnaire 3 days after discharge and every month until PACD. The EQ-5D-5L will be administered using the Unify™ mobile software application. Analysis and reporting of the EQ-5D-5L data will be presented in a separate report.

AZ (or those acting on behalf of AZ) will set-up clinical sites and invite site staff to use Unify™ by email but will not have the ability to view any patient level system data during the trial. Any data collected will be used for Unify™ system functionality only and is not considered to be CT data.

AZ will own any system data collected which may be used after the trial to make improvements to Unify™. System data collected will be retained for a period of 10 years after trial closure.

The use of the Unify™ mobile software application is optional for the patient and captured in the ICF.

In February 2023, it was decided that the composite of HHF or CV death will no longer be the primary endpoint, but the endpoint reporting functionality of those events will continue. It was also decided to remove PACD from the study. As a consequence, patients (only active users of Unify application) will be asked to complete the EQ-5D-5L questionnaire every month until their individual closing visit, instead of until PACD.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

To control the overall type I error rate at 5% 2-sided, the significance level will be adjusted for one interim analysis of efficacy performed by the DMC. For the primary endpoint the following null hypothesis will be tested at the 4.98% 2-sided significance level:

H0: Win-Ratio [dapagliflozin:placebo] = 1

versus the alternative hypothesis

H1: Win-Ratio [dapagliflozin:placebo] ≠ 1

In February 2023, it was decided to remove the efficacy interim analysis and to test the primary endpoint at 5% 2-sided significance level at the end of the study.

9.2 Sample Size Determination

The primary objective of the study is to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio of 0.80 between dapagliflozin and placebo, using a 2-sided alpha of 4.98% (adjusted for interim analysis), 722 patients with primary endpoint events will provide a statistical power of 85% for the test of the primary composite endpoint. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The assumed HR of 0.80 is considered as clinically relevant and has taken into account the HF outcomes in the MI sub-group in the DECLARE trial. The critical hazard ratio for achieving statistical significance is estimated to be 0.864.

The study is event-driven. With an estimated annual placebo event rate of 7.5% (from an observational database within the SWEDEHEART registry) for the primary composite endpoint, 6400 patients are estimated to provide the required number of primary events, based on an anticipated accrual period of 18 months and a total study duration of approximately 30 months, and considering an estimated annual drop-out rate at 1% during the study. The sample size, duration of recruitment period, and total study duration may change depending on the recruitment rate and event rate of the primary endpoint.

In February 2023, the primary objective of the study was revised to determine if the clinical benefit of dapagliflozin is superior in relation to placebo and this objective will be assessed with a hierarchical composite endpoint and analysed using the win-ratio method. Assuming a true win-ratio of 1.20 between dapagliflozin and placebo, 4000 patients will provide a statistical power of 80%, based on simulations, for the test of the primary composite endpoint, using a 2-sided alpha of 5%. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The assumed win-ratio of 1.20 is considered clinically relevant.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Full analysis set (Intention to Treat principle)

All patients who have been randomised to study treatment will be included in the Full Analysis Set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised IP assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the primary and secondary efficacy variables and for the exploratory efficacy variables.

Safety analysis set

All randomised patients who received at least one dose of study treatment will be included in the safety population. Patients will be analysed according to the treatment actually received. For any patients given incorrect treatment, ie, randomised to 1 of the treatment groups but

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

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

9.4 Statistical Analyses

The statistical analysis plan will be finalised prior to data base lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

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

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the intention to treat (ITT) principle using the FAS, including events with onset on or prior to PACD, adjudicated and confirmed by the CEC committee.

In the analysis of the primary composite endpoint, treatments (dapagliflozin versus placebo) will be compared using a Cox proportional hazards model with a factor for treatment group, stratified by country.

The individual components included in the primary composite endpoint will also be analysed separately, in the same way as the composite. Analyses of CV death, either as a component of a composite or on its own, will include deaths adjudicated as CV cause as well as deaths adjudicated as undetermined cause.

Kaplan-Meier (KM) estimates of the cumulative proportion of patients with events will be calculated and plotted per treatment group, with the number of patients at risk indicated below the plot at specific time points.

In February 2023, it was decided to remove PACD from the study, and as a consequence, all data collected on or before each patient's individual closing visit will be considered. Also, the primary endpoint was revised to a hierarchical composite endpoint consisting of the following components in the following order of clinical importance: Death, HF events, non-fatal MI,

Atrial fibrillation/flutter events, new onset of T2DM, symptoms of HF as measured by NYHA class at last visit, as well as body weight loss at least 5% at last visit. The primary endpoint will be assessed using the win-ratio method and each patient in the treatment group will be compared with each patient in the control group to determine the winner/loser/tie within each pair across the multiple outcomes. The win-ratio and corresponding 95% confidence interval will be reported.

9.4.2.2 Secondary Endpoint(s)

The secondary variables are the time to first event included in the composite endpoint of CV death, MI and stroke, time to first fatal or non-fatal MI, time to death of any cause, time to CV death and new onset type 2 diabetes. The secondary analyses will be based on the ITT principle using the FAS, using MIs and strokes as reported by the investigators, and CV death as adjudicated and confirmed by CEC.

The secondary variables will be analysed in the similar manner as the primary variable.

In February 2023, the following was decided:

The key secondary endpoint will be the same as the primary endpoint, but only with 6 components excluding the body weight component and will be analysed in the similar manner as the revised primary endpoint.

The composite of HHF and CV death was added as a secondary composite endpoint.

Time to hospitalisation for any cause was added as a secondary endpoint.

Change from baseline to last visit in body weight was added as a secondary endpoint.

9.4.2.3 Tertiary/Exploratory Endpoint(s)

Analyses for the exploratory endpoints will be defined in the statistical analysis plan (SAP).

9.4.2.4 Withdrawal From Study/Study Drug, Intercurrent Events and Estimand

It is important to distinguish between non-adherence with, or withdrawal from, randomised treatment and discontinuation from the trial. A randomised patient can withdraw from the study but not from the analysis, and according to the intention to treat principle, all data will be included. The potential impact of intercurrent events (events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation [eg, discontinuation of treatment, switching treatment, terminal events such as death, lost to follow-up or withdrawn consent]) is anticipated to be low and with even distribution between the treatment arms. The primary and secondary objectives are event-based and will be evaluated under the treatment policy estimand to reflect the effect of the initially assigned randomised study drug, irrespective of adherence to randomised study treatment. Specifically,

the analyses will be performed for the full analysis set including all events that occurred on or prior to PACD, including events following premature discontinuation of study drug.

In February 2023, it was decided that the analyses will be performed for the full analysis set including all data collected on or prior to the date of each patient's individual closing visit.

9.4.2.5 Subgroups

Subgroups of special interest will be pre-specified in the SAP. Subgroup analyses for primary and secondary efficacy endpoints will be assessed using the Cox regression model.

In February 2023, this section was updated to read:

Subgroups of special interest will be pre-specified in the SAP. Subgroup analyses for primary and key secondary efficacy endpoint as well as for the composite of HHF or CV death (secondary endpoint) will be assessed.

9.4.3 Safety

The number and percent of patients with AEs leading to hospitalisation or death, will be summarised by treatment group. For safety analyses, summaries will be provided using both on-treatment observations and using all observations regardless of whether patients are on or of study treatment.

9.4.4 Methods for Multiplicity Control

The significance level of alpha to be used for the final analysis will be adjusted for the interim analysis to control the overall type I error at 0.05 (2-sided). The primary endpoint will be tested for the final analysis at a 2-sided alpha level of 0.0498. Multiplicity across primary and secondary endpoints will be accounted for by utilising a pre-specified hierarchical order of the primary and secondary endpoints. The secondary all-cause mortality endpoint will be tested outside the multiple testing procedure. A separate alpha spending function will be used for the secondary endpoints. For more details around multiplicity see SAP.

In February 2023, this section was revised. The primary endpoint will be tested at a 2-sided alpha level of 0.05. Multiplicity across primary and secondary endpoints will be accounted for by utilising a pre-specified hierarchical order of the primary and secondary endpoints. The secondary all-cause mortality endpoint will be tested outside the multiple testing procedure. For more details see SAP.

The secondary endpoints will be tested in the same order as listed in table 3, objectives and endpoints.

9.5 Interim Analyses

An interim analysis is planned to be performed when approximately 2/3 of the primary events have been adjudicated. The interim analysis will assess superiority of dapagliflozin to placebo. The interim analysis will use a 1-sided alpha level of 0.001. At the interim analysis, the primary composite endpoint will be first tested at the specified alpha level. If superiority is achieved for the primary endpoint, then the superiority of dapagliflozin to placebo on CV death will be tested at a 1-sided alpha level of 0.001. If CV death also is significant, and with an appropriate margin, then an action is triggered whereby the DMC will evaluate the totality of the available efficacy data and safety data, to determine if benefit is unequivocal and overwhelming such that the DMC recommends ending the study. See SAP for more details.

In February 2023, it was decided to remove the efficacy interim analysis from the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AZ will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation but the accountability remains with AZ.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [IB or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.

  - A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Dissemination of Clinical Study Data

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

A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF (either transferred from the registry or entered manually) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 7 Guidance for Definition of Acute Myocardial Infarction and Stroke

Guidance for Definition of Acute Myocardial Infarction

The definition is based on Fourth Universal MI definition (Thygesen et al 2019). The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any 1 of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the 99th percentile upper reference limit (URL) and with at least 1 of the following:
  - Symptoms of ischaemia
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- PCI-related MI is arbitrarily defined by elevation of cTn values (> 5 x 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling. In addition, either

  - symptoms suggestive of myocardial ischaemia, or
  - new ischaemic ECG changes, or
  - angiographic findings consistent with a procedural complication, or
  - imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile URL
- CABG- related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 x 99th percentile URL) in patients with normal baseline cTn values (≤ 99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Guidance for Definition of Stroke

The definition is based on the standardised definitions for endpoints (Hicks et al 2015). Stroke is defined as an acute episode of focal or global neurological dysfunction caused by cerebral vascular injury as a result of infarction or haemorrhage not caused by trauma. Investigators will classify strokes into 1 of 3 mutually exclusive categories: ischaemic, haemorrhagic, or undetermined. Whenever possible, stroke diagnoses should be confirmed using neuroimaging (CT or MRI) to minimise the number of strokes classified as "undetermined".

Ischaemic Stroke

An acute episode of focal cerebral dysfunction caused by cerebral infarction. Either of the following is considered to be an ischaemic stroke:

- Rapid onset (or existence on awakening) of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischaemic aetiology (not associated with brain infection, trauma, tumour, seizure, severe metabolic disease, or degenerative neurological disease)
- Rapid worsening of an existing focal neurological deficit (eg, the index stroke event) that is judged by the Investigator to be attributable to a new infarction or extension of a previous infarction in the same vascular bed, based on persisting symptoms or imaging evidence of infarction and no evidence of a non-ischaemic aetiology. In case imaging is inconclusive, persistent symptoms is defined as duration of ≥ 24 hours or until death

Haemorrhagic Stroke

An acute episode of focal or global cerebral dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage not caused by trauma. Subdural haematomas are ICH events but not strokes.

Undetermined Category of Stroke

An acute episode of focal or global neurological dysfunction caused by presumed brain vascular injury as a result of haemorrhage or infarction but with insufficient information to allow categorisation as either ischaemic or haemorrhagic. Strokes of undetermined category will be analysed as ischaemic strokes.

References:

Thygesen et al. European Heart Journal (2019) 40, 237–269.

Hicks et al. Circulation (2015) 132(4):302-61.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Monitoring Plan.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant consented and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant,
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

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

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. The investigator should assist and facilitate transferal of participants to another site for follow up in the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent 1 of the outcomes listed above.

AEs for **malignant tumours** reported during a study should generally be assessed as **S**AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

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

Intensity Rating Scale

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AZ would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AZ study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognised that could have led to an error

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)
- Wrong drug administered to participant (excluding IRT errors)

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to 1 of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or SoC medication in open label studies, even if an AZ product

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

The investigator is responsible for recording data pertaining to Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

Appendix C Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndromes
ARB	Angiotensin receptor blockers
AZ	AstraZeneca
β-hCG	Beta human chorionic gonadotropin
BMI	Body Mass Index
BP	Blood pressure
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CEC	Clinical Endpoint Committee
CI	Confidence interval
CKD	Chronic kidney disease
COVID-19	Coronavirus Disease of 2019
CRF	Case report form
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical study report
CT	Clinical trial
cTn	Cardiac troponin
CV	Cardiovascular
DBL	Data base lock
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
DMC	Data Monitoring Committee
EASD	European Association for the Study of Diabetes
EC	Executive Committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D-3L	EuroQol five-dimensional three-level questionnaire
EQ-5D-5L	EuroQol five-dimensional five-level questionnaire
ESC	European Society of Cardiology
FAS	Full Analysis Set

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
HbA1c	Glycosylated haemoglobin
HF	Heart Failure
HFrEF	Heart Failure and reduced Ejection Fraction
HHF	Hospitalisation for Heart Failure
HR	Hazard ratio
I/E	Inclusion/Exclusion
IB	Investigator's Brochure
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention to treat
IUS	Intrauterine hormone-releasing system
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MINAP	The UK-based Myocardial Ischaemia National Audit Project
MRA	Mineralcorticoid receptor antagonist
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICOR	The National Institute for Cardiovascular Outcomes Research
Non-ST	non-ST segment elevation myocardial infarction
NSTEMI	non-ST segment elevation myocardial infarction
NYHA	New York Heart Association
PACD	Primary analysis censoring date
PCI	Percutaneous coronary intervention
PCSK-9	Proproteins convertase subtilisin/kexin type 9
PSSR	Project Specific Safety Requirements
PTDV	Premature treatment discontinuation visit

Abbreviation or special term	Explanation
QD	Once daily
RISK-HIA	The national registry of acute cardiac care
R-RCT	Registry-based randomised controlled trial
RRR	Relative Risk Reduction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCV	Study Closure Visit
SEPHIA	The national registry of secondary prevention
SGLT2	Sodium glucose co-transporter 2
s-LDL	serum low-density lipoprotein
SoA	Schedule of Activities
SoC	Standard of Care
ST	STEMI - elevation myocardial infarction
STEMI	ST segment elevation myocardial infarction
s-TG	serum triglycerides
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UCR	Uppsala Clinical Research Center
UK	United Kingdom
URL	Upper reference limit

Appendix D EQ-5D-5L Health Questionnaire

English verison for the UK

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

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

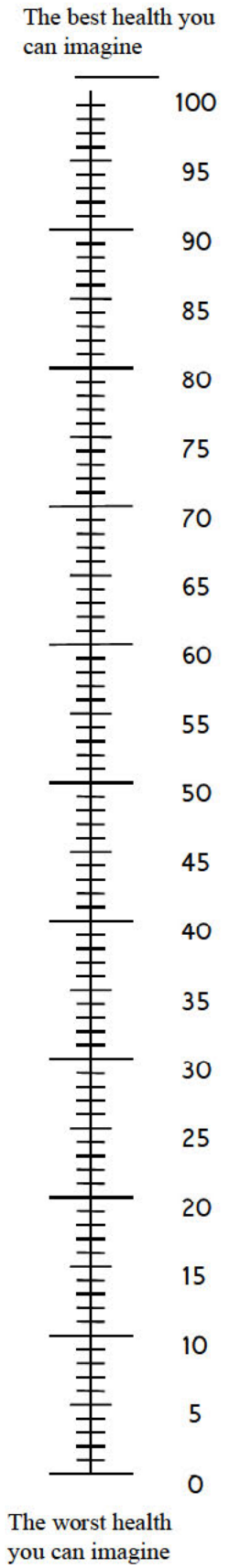
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix E Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 25-May-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The amendment extends the randomisation window to allow randomisation of patients within 10 days after MI and includes additional information on awareness of ketoacidosis. The amendment also contains information on an additional option for study drug delivery to patients due to the COVID-19 pandemic. At the same time minor clarifications and editorial changes have been made.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Figure 1 Study Design	Extending randomisation window.	Extending randomisation window to 10 days, if earlier randomisation is not feasible.	Substantial
Table 1 Schedule of Activities	Extending randomisation window.	Extending randomisation window to 10 days, if earlier randomisation is not feasible.	Substantial
Table 1 Schedule of Activities	Removal of 'coronary angiography'. EQ-5D-5L questionnaire completion clarification.	Additional clarification statements.	Non-substantial
Table 2 Risk Assessment	Clarification of inclusion criterion 4.	To clarify the emphasis is on symptoms of hypotension, not single blood pressure readings.	Substantial
Section 5.1 Inclusion Criteria	Addition to inclusion criterion 2.	Extending randomisation window to 10 days, to allow patients with MI to be randomised within 10 days.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.1 Inclusion Criteria	Clarification of inclusion criterion 4.	To clarify the emphasis is on symptoms of hypotension, not single blood pressure readings.	Substantial
Section 5.2 Exclusion Criteria	Addition to exclusion criterion 1.	To include information on awareness of ketoacidosis.	Substantial
Section 6.2 Preparation/Handling/Storage of Interventions	Additional option of study drug delivery to patient due to the COVID-19 pandemic.	To include information about option of study drug delivery to patient's home during COVID-19 pandemic.	Non-substantial
Section 6.3.1 Emergency Unblinding	Clarification.	Clarification that individual treatment codes, indicating the treatment allocation for each randomised patient, will be available from the IRT to the Investigator(s) only.	Non-substantial
Section 6.5.2 Background Medication	Clarification.	Clarification statement.	Non-substantial
Section 6.5.5 Invasive Cardiac Procedures	Removal of 'coronary angiography'.	Clarification statement.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Clarification of discontinuation option if a patient develops T1DM during the trial.	To clarify patients with T1D should permanently discontinue study drug.	Non-substantial
Section 7.1.5 Ketoacidosis in patients with type 2 diabetes mellitus	Additional Section with information regarding ketoacidosis in patients with type 2 diabetes mellitus.	To include information on awareness of ketoacidosis.	Substantial
Section 7.2 Participant Withdrawal from the Study	Removal of wording related to withdrawal from registry.	Statement not applicable.	Non-substantial
Section 8.3.10.1 Maternal Exposure	Revised wording related to congenital anomalies	Change to align with regulatory requirements.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	("congenital anomaly" instead of "congenital abnormality").		
Section 8.9.2 Visit 1: Screening and Randomisation (Day 1)	Adding clarification that the first IP dose is intended to be taken on the randomization day.	Clarification statement.	Non-substantial
Section 8.9.3 Visit 2: Early Follow-visit, Week 8 (±14)	Removal of 'coronary angiography'.	Clarification statement.	Non-substantial
Section 8.9.4 Visit 3: The Second Follow-up Visit, Year 1 (±1 month)	Correction of visit window. Removal of 'coronary angiography'.	Clarification. Clarification statement.	Non-substantial
Section 8.9.5 Visit 4, 5, 6 etc: Study-specific Visit(s), Month 22 (±1 month) and Thereafter Occurring Every 10th Month Until Study Closure Visit	Correction of visit window. Removal of 'coronary angiography'.	Clarification. Clarification statement.	Non-substantial
Section 8.9.6 Premature Treatment Discontinuation Visit	Removal of 'coronary angiography'.	Clarification statement.	Non-substantial
Section 8.9.7 Study Closure Visit	Removal of 'coronary angiography'.	Clarification statement.	Non-substantial
Appendix A 3 Informed Consent Process	Removal of rescreening information.	To align with study design.	Non-substantial
Appendix A 5 Dissemination of Clinical Study Data	Clarification on website address.	Clarification.	Non-substantial
Appendix B 2 Definitions of Serious Adverse Event	Revised wording related to congenital anomalies ("congenital anomaly" instead of "congenital abnormality").	Change to align with regulatory requirements.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

Amendment 2 14-Dec-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The amendment provides changes in inclusion criteria to broaden the study population to also include patients with impaired regional or global LV systolic function without numerical cut-off LVEF <50%. At the same time minor clarifications have been made.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.1 Synopsis	Addition of sentence that the sample size, duration of recruitment period, and total study duration may change depending on the recruitment rate and event rate of the primary endpoint.	The recruitment at the beginning of the study was slower than expected, therefore it is possible that recruitment period and study duration might be extended.	Non-substantial
1.2 Study Design	Change in the study scheme to replace "Reduced LVEF or Q-wave" into "Impaired LV systolic function or Q-wave".	Due to the change in inclusion criterion 3 (inclusion of the patients with impaired regional or global LV systolic function at any timepoint without cut-off LVEF <50%).	Non-substantial
4.6.2.1 Scope	Clarification on MINAP registry in Scotland.	The country of Scotland has started participating in the study.	Non-substantial
Section 5 Study population and Section 5.1 Inclusion Criteria	Inclusion of patients with impaired regional or global LV systolic function at any timepoint without cut-off LVEF <50%.	The experience in the study is that echocardiography reports frequently quantifies the measured ejection fraction in intervals (eg. 45-50% or 50-55%) although there are findings of impaired	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		regional wall motion. The cut off EF <50% was a risk enrichment strategy but seems to exclude a population of patients with impaired regional LV systolic function that could also benefit from the treatment. It has also been clarified that the investigation showing evidence of impaired regional or global LV systolic function can be performed at any timepoint during the MI related hospitalisation.	
Section 5.2 Exclusion Criteria	Removal of word 'serum' from description of the pregnancy testing type.	Clarification that pregnancy testing is not restricted to serum testing only.	Non-substantial
6.3 Measures to minimise bias	Removal of information on 30% capping from each country.	The addition of the country of Scotland to Wales and England representing the UK makes the capping of at least 30% from each country not possible due to imbalance in the study population basis.	Non-substantial
8.2. Safety assessments	Clarification on information that deaths in UK are captured by linkage with MINAP data, rather than by automatic transfer.	To correct information on deaths transferring to MINAP in UK, as it differs from the automatic data transfer to SWEDEHEART in Sweden.	Non-substantial
9.2 Sample size determination	Addition of sentence that the sample size, duration of recruitment period, and total study duration may change depending on the recruitment rate and	The recruitment at the beginning of the study was slower than expected, therefore it is possible that recruitment period and study duration might be extended.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	event rate of the primary endpoint.		

11 REFERENCES

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