Statistical Analysis Plan	
Study Code	D169DC00001
Edition Number	4.0
Date	19 June 2023

DAPA-MI

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
AF	Atrial Fibrillation
ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
CCS	Canadian Cardiovascular Society
CEC	Clinical Endpoint Committee
CI	Confidence Interval
COVID-19	Coronavirus Disease of 2019
CSP	Clinical Study Protocol
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
HbA1c	Glycosylated haemoglobin
HHF	Hospitalisation for Heart Failure
HF	Heart Failure
HR	Hazard Ratio
I/E	Inclusion/Exclusion
IP	Investigational Product
ITT	Intention To Treat
IxRS	Interactive Voice/Web Response System
KM	Kaplan-Meier
LTFU	Lost To Follow Up
LVEF	Left Ventricular Ejection Fraction
MACE (3-P MACE)	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
NA	Not Applicable
NSTEMI	Non-ST segment Elevation Myocardial Infarction
NYHA	New York Heart Association

Abbreviation or special term	Explanation
PD	Protocol Deviation
PT	Preferred Term
Q1	First Quarter
Q3	Third Quarter
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT2	Sodium-glucose co-transporter-2
SoC	Standard of Care
SOC	System Organ Class
ST	Sinus Tachycardia
STEMI	ST segment Elevation Myocardial Infarction
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UK	United Kingdom
WoC	Withdrawal of Consent

AMENDMENT HISTORY

Category: Change refers to	Version	Description of change	In line with the CSP?	Rationale
Other	1.0	First version published.	N/A	When first version of the SAP was published.
Other	2.0	Section 1.3. Updated Figure 1 Study Design.	Y(version 3.0)	To align with the study protocol.
Primary endpoint	2.0	Section 1.4. Added clarification regarding the sample size	Y(version 3.0)	To align with the study protocol.
Data presentations	2.0	Section 2.2. Added a few additional important protocol deviations.	N/A	To align with updated AstraZeneca SAP template.
Data presentations	2.0	Section 2.2. Information about COVID-19 related protocol deviations added	Y(version 3.0)	To summarise the effect of COVID-19 on the study protocol.
Secondary endpoint	2.0	Section 3. More specified description of the incidence of new onset T2DM (Time to the first occurrence).	Y(version 3.0)	To clarify what patients will be in the denominator.
Data presentations	2.0	Section 4.1. Clarified baseline definition for weight and HbA1c. Added minimum and maximum for how Clever Cap will be summarised.	N/A	To clarify what the baseline is for these variables and clarify how Clever cap will be analysed.

Other	2.0	Section 4.1.8, 4.2.7 T-test being replaced with a linear regression model containing treatment and country.	N/A	To align with the planned analysis/output
Primary and secondary endpoints	2.0	Section 4.1.4. Changed presentation of KM% from 2 year to 1 year. Applicable for all time to event analyses.	N/A	The median time in study has decreased due to the study delay.
Data presentations	2.0	Section 4.1.9. Clarified how the analysis of proportions is conducted and what will be presented from it.	N/A	To clarify how the analysis is carried out and what the output will be from it.
Other	2.0	Section 4.2.2. Added more detailed information about prohibited concomitant medication	Y(version 3.0)	To align with the study protocol
Primary and secondary endpoints	2.0	Section 4.2.3. Changed from score statistics to Wald statistics when evaluating p-values from Cox model. Thus p-values and 95% confidence intervals for the HR will be based on the Wald statistic.	N/A	To clarify how p-values and 95% confidence intervals for the HR will be calculated.
Other	2.0	Section 4.2.3. Removed text explaining about non-proportionality.	N/A	Pre-empt a possible interpretation of non-proportionality in absence of data.

Primary and secondary endpoints	2.0	Section 4.2.3.1. Table 1: Subgroups “Insulin, Oral Glucose lowering agent” merged to one subgroup “Anti-hyperglycemic agents”. Renamed subgroup “Oral Antiplatelets” to “Thienopyridine/Ticagrelor” Subgroup Removed subgroup “Diuretics” and “Angiotensin II receptor blocker” since not collected in UK at baseline. Added category LVEF 30-50 into the current LVEF subgroup.	N/A	Scientific interest
Primary and secondary endpoints	2.0	Section 4.2.3.1. Table 1: “Previous Hypertension ,Yes/No” inserted as a new subgroup characteristic in the table.	N/A	Scientific interest
Secondary endpoints	2.0	Section 4.2.3.1, 4.2.4. Subgroup analysis will also be conducted for the secondary endpoint “new onset of T2DM”.	N/A	Scientific interest
Primary endpoint	2.0	Section 4.2.3.2. Sensitivity analysis added regarding investigated reported primary events.	N/A	To assess the robustness of adjudication for the primary endpoint.

Primary endpoint	2.0	Section 4.2.3.2. Sensitivity analysis added regarding COVID-19.	N/A	To assess the robustness of the primary analysis in relation to COVID-19 related events.
Primary endpoint	2.0	Section 4.2.3.2. Sensitivity analysis added regarding the modified Hicks criteria for the primary endpoint.	N/A	To assess the robustness of modified Hicks criteria for the primary endpoint.
Primary endpoint	2.0	Section 4.2.3.2. Added text around a possible sensitivity analyse to investigate the influence and magnitude of incomplete dates.	N/A	Feedback from authorities
Data presentations	2.0	Section 4.2.6. Clarified how the components in the composite recurrent HF hospitalisation or CV death will be analysed.	N/A	To clarify how the LWYY analysis will be carried out.
Data presentations	2.0	Section 4.2.9.2. Section renamed to “Serious adverse events”. Added information how SAE will be collected in Sweden and UK.	Y(version 3.0)	To clarify how SAE will be collected in each country.
Data presentations	2.0	Section 4.2.9.3. Added reason why adverse event leading to discontinuation , interruption or dose	Y(version 3.0)	To align with study protocol.

		reduction is not collected in study.		
Data presentations	2.0	Section 4.2.9.5. Excluded S-Creatinine and eGFR since they are only collected at baseline. Added HbA1c, Body weight and BMI to be presented.	Y(version 3.0)	To clarify which parameters will be presented in laboratory and vital signs evaluation.
Data presentations	2.0	Added section 4.2.9.7 added summary of COVID-19 related AEs.	N/A	To investigate the influence of COVID-19 on AEs.
Data presentations	2.0	Section 4.2.10. Modified section text regarding EQ-5D-5L	N/A	Clarification about what output will be produced added.
Data presentations	2.0	Section 4.2.11. Modified section text regarding Unify app	N/A	Clarification about what output will be produced added.
Data presentations	2.0	Section 4.2.12. Modified section text regarding Clever Cap	N/A	Clarification about what output will be produced added.
Other	2.0	Section 1.3, 2.1, 3, 4.1, 4.1.1, 4.1.5-4.1.9, 4.2.1, 4.2.3, 4.2.7, 4.2.9, 7. Several minor classification, abbreviations added and removed, corrections and typos.	N/A	To help readability
Study title	3.0	Updated title	Yes (version 4.0)	To align with study protocol version 4.0

Study objectives (section 1.1)	3.0	Updated objectives and endpoints	Yes (version 4.0)	To align with study protocol version 4.0
Start of close-out period (former known as PACD) (section 1.2.1)	3.0	PACD was removed from study design and as a consequence the start of close-out period was re-defined	Yes (version 4.0)	To align with study protocol version 4.0
Vital status (section 1.2.4)	3.0	PACD was removed from study design and as a consequence the vital status at study end was re-defined	Yes (version 4.0)	To align with study protocol version 4.0
Study design (section 1.3)	3.0	The key study assumptions were updated	Yes (version 4.0)	To align with study protocol version 4.0
Number of patients (section 1.4)	3.0	The sample size calculation was updated as a consequence of changed study design	Yes (version 4.0)	To align with study protocol version 4.0
Primary and secondary variables (section 3)	3.0	The primary and secondary variables were updated and rearranged	Yes (version 4.0)	To align with study protocol version 4.0
Baseline for lab, physical examination and vital signs (section 4.1)	3.0	Baseline was re-defined	Yes (version 4.0)	To align with study set-up
Hypothesis (section 4.1.2)	3.0	Efficacy interim analysis was removed, and hypothesis endpoint was updated from HR to Win-Ratio	Yes (version 4.0)	To align with study protocol version 4.0

Confirmatory testing procedure (section 4.1.3)	3.0	Win-ratio endpoints were placed first and secondary endpoints were re-ordered	Yes (version 4.0)	To align with study protocol version 4.0
Presentation of win-ratio analysis (section 4.1.4)	3.0	New section added to describe the win-ratio analysis	Yes (version 4.0)	To align with study protocol version 4.0
Vital status and follow-up of endpoints (section 4.1.6)	3.0	PACD was removed from study design and as a consequence the close-out period was re-defined	Yes (version 4.0)	To align with study protocol version 4.0
Analysis of last assessment for continuous variables (section 4.1.8)	3.0	Section removed as no such analyses will be performed	Yes (version 4.0)	To align with study protocol version 4.0
Analysis of the primary efficacy variable and the key secondary endpoint (section 4.2.3)	3.0	New section added to describe analysis method for win-ratio endpoints	Yes (version 4.0)	To align with study protocol version 4.0
Subgroup analysis (section 4.2.4.1)	3.0	Subgroups updated and endpoints for which subgroup analysis will be performed for updated	Yes (version 4.0)	To align with study protocol version 4.0
Analysis of other secondary endpoints (section 4.2.5)	3.0	Update of other secondary endpoints	Yes (version 4.0)	To align with study protocol version 4.0
Analysis of exploratory time to event variables (section 4.2.6)	3.0	Update of exploratory endpoints	Yes (version 4.0)	To align with study protocol version 4.0
Analysis of change from baseline (section 4.2.8)	3.0	Update for which variables this analysis will be performed for	Yes (version 4.0)	To align with study protocol version 4.0
Interim analysis (section 5)	3.0	Interim analysis removed	Yes (version 4.0)	To align with study protocol version 4.0

References (section 7)	3.0	List of references updated	Yes (version 4.0)	To align with study protocol version 4.0
All sections	3.0	Several minor updates, corrections and typos	Yes (version 4.0)	To align with study protocol version 4.0
Endpoints	4.0	Added the secondary composite endpoint of CV death, HHF and MI	No	Of scientific interest
Win-ratio method	4.0	Added analysis details	No	To make the analysis method clearer

1 STUDY DETAILS

1.1 Study objectives

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 demonstrate the superiority of dapagliflozin 10 mg once daily (QD) versus dapagliflozin 10 mg placebo to match in reducing the incidence of CV	Time to the first occurrence of any of the components of this composite: • HHF

Objectives	Endpoints
death, HHF or MI when added to SoC in non-diabetic patients with myocardial infarction and impaired left ventricular systolic function during the index MI hospitalisation*	• CV death • MI
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	
CCI	
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

*The objective/composite endpoint of CV death, HHF or MI has not been specified in the protocol and is included here for the purpose of being included in the confirmatory testing (section 4.1.3).

1.2 Definitions

1.2.1 Start of close-out period

The executive committee and AstraZeneca 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 close-out visits.

The analyses of the primary endpoint will include all data collected during the study up until, and including, each patient's individual closing visit.

1.2.2 Withdrawal of consent

Withdrawal of consent (WoC) means withdrawal from study and should only occur if the patient does not agree to any kind of further assessment at all. No data after date of WoC should be collected, with the exception for vital status (dead or alive) at the end of the study collected from public sources, which will be included in the analysis of death from any cause as a sole outcome and in patient disposition summaries. Data collected on or prior to date of WoC will be included in analyses.

1.2.3 Discontinuation from study drug

Discontinuation from study drug does not mean WoC. Optimally, patients who discontinue from study drug should continue study visits according to plan until study closure. Alternatively, if the patient does not agree to this approach, modified follow-up should be arranged. Data from patients who did not withdraw consent will be included in the intention to treat (ITT) analyses irrespective of whether events occur before or following discontinuation of study drug.

1.2.4 Vital status

The vital status at the end of the study is considered to be known if a patient is dead or alive at their individual closing visit. If not possible to determine if a patient is dead or alive at their individual closing visit, the vital status for such patients will be considered to be unknown. For patients who have withdrawn consent, the investigator will attempt to collect vital status

from publicly available sources at study closure in compliance with local privacy laws/practices.

1.2.5 Lost to follow-up

The term lost to follow-up (LTFU) will be limited to patients with unknown vital status at the end of the study as defined in Section 1.2.4. Other measures will be used to describe incomplete follow-up (Section 4.1.6).

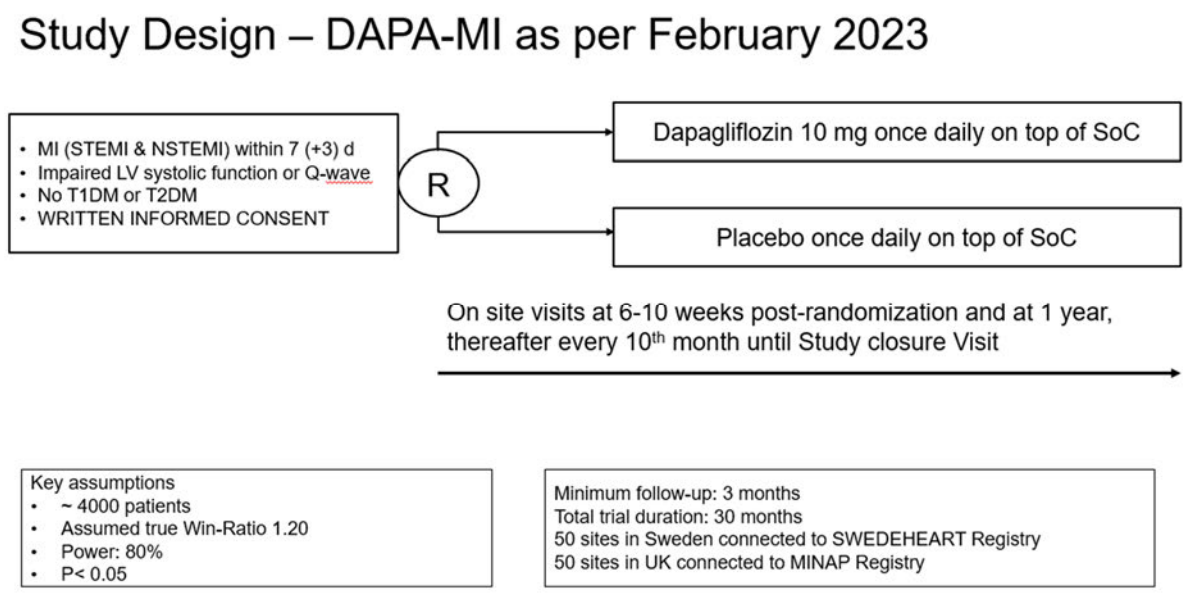
1.3 Study design

This is a multicentre, parallel group, 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 approximately 4000 patients. In the study the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care (SoC) therapy will be evaluated for clinical benefit.

The anticipated duration of the study is approximately 30 months. The study closure procedures will be initiated when approximately 4000 patients have been randomised.

Patients will be randomised 1:1 to either dapagliflozin 10 mg or placebo.

Randomisation will be performed in balanced blocks of fixed size, stratified by country. The randomisation codes will be computer generated and loaded into the IxRS (Interactive Voice/Web Response System) database.



1.4 Number of patients

The primary objective of the study is 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. With a study duration of approximately 30 months and a minimum follow-up of 3 months, 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 two-sided with type I error of 5%. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The assumed win-ratio of 1.20 is considered as clinically relevant (if the observed win-ratio is 1.20 then the likelihood for a better outcome with Dapagliflozin is 20% higher compared to Placebo).

The assumptions for the simulations are described below. Assumed effect sizes are based on historical data for related subgroups in Dapagliflozin outcome studies DECLARE, DAPA-HF, DAPA-CKD and DELIVER.

1. All-cause mortality: around 55 patients with event and an assumed risk ratio Dapagliflozin versus Placebo around 0.89
2. Heart failure events: around 70 patients with event and an assumed risk ratio Dapagliflozin versus Placebo around 0.74

3. Non-fatal MI: around 50 patients with event and an assumed risk ratio Dapagliflozin versus Placebo around 0.84
4. Atrial fibrillation/flutter event: around 35 patients with event and an assumed risk ratio Dapagliflozin versus Placebo around 0.86
5. New onset of T2DM: around 70 patients with event and an assumed risk ratio Dapagliflozin versus Placebo around 0.75
6. NYHA class at last visit: all patients will participate in the analysis (if no event for the first 5 endpoints in the hierarchy) and the assumption is that patients in the Dapagliflozin arm will have a 12% lower risk of developing worse symptoms of HF as measured by NYHA class as compared with patients in the Placebo arm.
7. Body weight loss at least 5% at last visit: around 725 patients and an assumed risk ratio Dapagliflozin versus Placebo around 1.13

2 ANALYSIS SETS

2.1 Definition of analysis sets

Patients could by error have been randomised more than once. Such patients will be analysed according to their first randomisation assignment. Serious adverse events (SAEs), study medication and endpoints will be consolidated and re-entered at the discretion of the Investigator under the patient identifier used in the first randomisation. The redundant records associated with the same patients will be stored in a separate dataset for future references.

Full analysis dataset

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 investigational product (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 dataset

All randomised patients who received at least 1 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, i.e. randomised to one 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.

2.2 Violations and deviations

The important protocol deviations listed below will be summarised by randomised treatment group

- Patients who were randomised but did not meet inclusion and exclusion criteria
- Patients who received the wrong study treatment at any time during the study
- Patients who received prohibited concomitant medication
- Written informed consent not obtained prior to mandatory study specific procedures, sampling, and analyses
- Those who developed discontinuation of protocol specified therapy criteria during the study, but remained on protocol specified therapy
- Site procedure for unblinding the subject is not compliant with CSP

Patients meeting criteria for important protocol deviations will be identified prior to unblinding. As the primary analysis is intention-to-treat analysis, important protocol deviation will not imply exclusion from the primary analysis.

All protocol deviations (PDs) related to COVID-19 will also be summarised. In order to allow easy filtering and reporting of COVID-19 related PDs (Important PD and Non-Important PD) issues must start with “COVID19” prefix recorded in CTMS in description field, followed by regular description of occurred case.

3 PRIMARY AND SECONDARY VARIABLES

Adjudication

Adjudication will only be performed for CV death and HHF. Potential events and event dates will be adjudicated by an independent clinical event adjudication committee (CEC). The committee members will not have access to the treatment codes for any patient. The CEC procedures and event definitions will be described in the CEC charter.

Time to event analyses

For analysis of time to first event, data will be expressed as two variables:

- A binary variable indicating whether the event in question occurred, or the patient was censored.
- An integer variable for the number of days from randomisation to the first occurrence of an event (start date of the event – randomisation date + 1), or for event free patients, from randomisation to censoring (censoring date – randomisation date + 1).

Clinical event assessment

Last clinical event assessment is defined as the last date when a patient was assessed for any potential events. It is expected that patients alive and under study follow-up will have a clinical event assessment at their individual study closure visit.

Primary variable

- The hierarchical composite of death, heart failure events, non-fatal MI, atrial fibrillation/flutter event, new onset of T2DM, NYHA class at last visit and body weight decrease at least 5% at last visit, based on the hierarchical order of clinical importance.

Each patient will be represented by its most severe event, according to the below ordering. In general, an event will lose compared with no event and an earlier event will lose compared with a later event (within the same category). For each pair-wise comparison, only events occurring within the shared follow-up time will be considered, i.e., the minimum follow-up time within each pair, resulting in censoring at the shared follow-up time for the patient with the longest follow-up time as it is unknown what would happen to the patient with shorter follow-up time after that timepoint. The follow-up time for each patient will be defined as time from randomisation to the following dates in the following order, if present:

1. Date of withdrawn consent
2. Date of death
3. Date of last clinical event assessment

4. Date of individual close-out visit

Death: Adjudicated cause of death will be used. CV death will lose compared with non-CV death.

- CV death < non-CV death < alive (time to event will differentiate if comparing two patients with event within the same category)

HHF: Investigator reported hospitalisation for heart failure defined as primary cause or contributing factor for hospitalisation, as assessed by investigator. Adjudicated HHF will lose compared with investigator reported HHF.

- Adjudicated HHF < investigator reported HHF < no HHF (time to event will differentiate if comparing two patients with event within the same category)

Non-fatal MI: Investigator reported MIs in CIEVENT CRF form.

- Event < no event (time to event will differentiate if comparing two patients with event)

AF/Flutter event: SAE leading to hospitalisation with a preferred term of atrial fibrillation or atrial flutter regardless of medical history at baseline will be included.

- Event < no event (time to event will differentiate if comparing two patients with event)

New onset of T2DM: Investigator reported cases with new diagnosis of type 2 diabetes reported on the DMDIAG CRF form after the index hospitalisation will be included.

- Event < no event (time to event will differentiate if comparing two patients with event)

NYHA class at last visit: NYHA class 0 and I will be in the same category as hard to differentiate. Last visit is defined as the last visit with NYHA measurement available, within each pair-wise comparison. Only measurements after the index hospitalisation will be considered. A pair-wise comparison including missing data at this level will result in a tie.

- Class IV < class III < class II < class 0/I

Body weight decrease (vs. baseline) of at least 5% at last visit: Last visit is defined as the last visit with body weight measurement available, within each pair-wise comparison. Only measurements after the index hospitalisation will be considered. A pair-wise comparison including missing data at this level will result in a tie.

- No decrease at least 5% < decrease at least 5%

Key secondary variable

- The hierarchical composite of death, heart failure events, non-fatal MI, atrial fibrillation/flutter event, new onset of T2DM and NYHA class at last visit, based on the hierarchical order of clinical importance.

Other secondary variables

- The incidence of HHF or CV death (Time to the first occurrence of any of the components)

  All adjudicated events from randomisation until WoC or each patient's individual closing visit (whatever occurs first) will be included. Patients without events will be censored at the earliest of date of WoC or non-CV death, and otherwise at the date of last clinical event assessment.

- The incidence of CV death, HHF or MI (Time to the first occurrence of any of the components)

  All events from randomisation until WoC or each patient's individual closing visit (whatever occurs first) will be included. Patients without events will be censored at the earliest of date of WoC or death, and otherwise at the date of last clinical event assessment.

- The incidence of hospitalisation for any cause (Time to the first occurrence of any of the components) (SAEs that requires or prolongs hospitalisation as collected at the SERAE CRF form)

  All events from randomisation until WoC or each patient's individual closing visit (whatever occurs first) will be included. Patients without events will be censored at the earliest of date of WoC or death, and otherwise at the date of last clinical event assessment.

- The incidence of new onset type 2 diabetes mellitus (T2DM) (Time to the first occurrence)

  Defined as reporting of new onset T2DM after discharge from the index hospitalisation as reported by investigators in the dedicated CRF form (DMDIAG).

  All events from randomisation until WoC or each patient's individual closing visit (whatever occurs first) will be included. Patients without events will be censored at the

earliest of date of WoC or death, and otherwise at the date of last clinical event assessment.

- The incidence of MACE (CV death, MI and stroke) (Time to the first occurrence of any of the components)

  MI will include investigator reported non-fatal and fatal MI. Stroke will include investigator reported non-fatal and fatal stroke. All events from randomisation until WoC or each patient's individual closing visit (whatever occurs first) will be included. Patients without events will be censored at the earliest of date of WoC or non-CV death, and otherwise at the date of last clinical event assessment.

- The change from baseline to last visit in body weight

  All data after the index hospitalisation until WoC or each patient's individual closing visit (whatever occurs first) will be considered. These analyses will be done for the on-treatment period and will include measurements on or after first dose of randomised study drug and on or before 30 days after last dose of study drug.

- The incidence of fatal or non-fatal MI (Time to the first occurrence)

  All investigator reported events from randomisation until WoC or each patient's individual closing visit (whatever occurs first) will be included. Patients without events will be censored at the earliest of date of WoC or death, and otherwise at the date of last clinical event assessment.

- The incidence of CV death (Time to occurrence)

  CV death will include CV deaths and deaths with undetermined cause of death, as adjudicated by the CEC. All events from randomisation until WoC or each patient's individual closing visit (whatever occurs first) will be included. Patients without events will be censored at the earliest of date of WoC or non-CV death, and otherwise at the date of last clinical event assessment.

- The incidence of all-cause mortality (Time to occurrence)

  All events from randomisation until each patient's individual closing visit, including deaths after WoC, will be included. Patients without events will be censored at the date last known alive.

Causes of deaths

The causes of deaths, as adjudicated by the CEC, will include CV cause, non-CV cause, and undetermined cause. 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.

Potential death cases found in publicly available sources after withdrawal of consent will not be adjudicated.

Non-fatal MI and non-fatal stroke

MI is defined as fatal if patient dies due to CV cause (according to CEC adjudication) within 30 days after onset of AE. Non-fatal MIs are all investigator reported MI that are not fatal.

Stroke is defined as fatal if patient dies due to CV cause (according to CEC adjudication) within 30 days after onset of AE. Non-fatal strokes are all investigator reported stroke that are not fatal.

Safety variables and collection of safety data

The safety variables are adverse events (AEs) leading to death or hospitalisation (Summary statistics)

The safety events will be collected from randomisation until and including the patient's last visit.

CEC will adjudicate deaths and HHF. If not adjudicated as HHF the event will be considered as an AE. All deaths will be considered as endpoints. For MI and Stroke, the investigator will decide if it is an endpoint. No events that are considered to be endpoints will be reported to health authorities to avoid unnecessary unblinding of efficacy endpoints.

4 ANALYSIS METHODS

All statistical analyses will be performed using the SAS® statistical analysis system (SAS Institute Inc., Cary, NC) and, where appropriate, additional validated software.

4.1 General principles

95% confidence intervals for the point estimates will be provided, without multiplicity adjustment as they will be interpreted descriptively and used as a measure of precision. All p-values will be unadjusted. P-values for variables not included in the confirmatory testing sequence or following a non-significant test in the sequence will be regarded as nominal. All p-values will be presented as 2-sided.

Incomplete dates

All efforts should be made to obtain complete dates of clinical assessments and events. For analyses requiring complete dates, partially missing dates will be imputed based on available corroborating information. Absence of any additional corroborating information, partially missing dates will be imputed as follows: if only the year part of a date is available (YY), then the date will be set to YY0701. If only the year and month is available (YYMM), then the date will be set to YYMM15. Additional imputation rules will be defined as appropriate to ensure that for example dates will not be imputed as prior to randomisation, after death, after WoC or end date before start date.

Special cases for date of death:

- For a patient that died with the date of death imputed, the maximum of the imputed date and last date the patient was known to be alive will be used as date of death.
- If adjudicated date of death is completely missing, the site-reported date of death will be used.

- For a patient that died that has a completely missing date of death, the last date the patient was known to be alive will be imputed and used as date of death.

Baseline for laboratory and physical examination/vital signs parameters

Baseline is defined as the last value on or before the date of randomisation. If no value is available, the last value on or before the day of discharge from the index hospitalisation will be used. Baseline values should be obtained during the index hospitalisation, with HbA1c as the only exception for which the measurements before the index hospitalisation but within 30 days prior to the randomisation are allowed.

Descriptive statistics

Numerical variables will be summarised using standard summary statistics including the number of patients, mean, standard deviation (SD), median, Q1, Q3 and range (i.e., minimum, and maximum) as appropriate. For categorical data, proportions will be presented in a frequency table format.

Study drug compliance

It will not be possible to calculate study drug compliance in this study due to no pill count. Instead, the number of times during the study that each patient opens (on or after date of randomisation and on or before the date of each patient's individual closing visit) the Clever Cap, will be summarized, including mean, median, maximum, minimum, quartiles and 5% and 95% percentiles will be calculated for each treatment arm for comparison.

4.1.1 Estimand for primary and secondary outcomes

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 (e.g., 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 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 data collected on or prior to each patient's individual closing visit, including data following premature discontinuation of study drug.

4.1.2 Hypotheses

For the primary and key secondary endpoints, the following null hypothesis will be tested at the 5% two-sided significance level

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

versus the alternative hypothesis

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

For the secondary time-to-event endpoints, the hypotheses will be in reference to hazard ratio rather than win ratio.

For the secondary endpoint of change in body weight, the hypotheses will be in reference to difference in mean absolute change from baseline.

4.1.3 Confirmatory testing procedure

The primary and secondary endpoints will be tested in the same order as listed in the objectives/endpoints table in section 1.1. In each step, the endpoint will be tested at full alpha, two-sided level of 0.05, and if meeting statistical significance, testing will continue to the next endpoint in order.

The secondary all-cause mortality endpoint will be tested outside the multiple testing procedure at a two-sided alpha level of 0.05, in consideration of the principles around testing of 'hard' endpoints as outlined O'Neill. (**Robert T. O'Neill, PhD 1997)**

4.1.4 Presentation of win-ratio analysis

For estimation of clinical benefit, the win-ratio and corresponding 95% confidence interval and p-value for confirmatory testing will be reported. Win-ratio is calculated as the ratio of the number of "winner" pairs to the number of "loser" pairs for the dapagliflozin arm.

The statistic represents the ratio of having a more favorable outcome versus a less favorable outcome when comparing the dapagliflozin group with the placebo group. If the estimated win-ratio is greater than 1 then the treatment effect is estimated to be in favors of dapagliflozin. The variance will be calculated by the method described by Yu et al, which is approximately the same as asymptotic normal U statistic approach. (Pocock et al 2012) (Yu et al 2022)

The results of the win-ratio analysis of the hierarchical composite endpoints will be tabulated and depicted. The contribution of the individual components will be described.

4.1.5 Presentation of time-to-event analyses

In general, summary tables of time-to-event analyses will include the number and percent of patients with event per treatment group, the 1-year KM rate, hazard ratio with 95% confidence interval and p-value.

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. The KM plots will be presented for all time to event analyses, including the individual components of the composite endpoints. (**Kaplan EL and Meier P 1958**). One year will be considered to be 360 days and one month will be considered to be 30 days. Specific time points for KM estimates will be the visit at week 8, the visit at 1 year, and the following visits at every 10 months.

A patient may have one or more events. For composite endpoints, the time to first event within the composite list will be used. For each component of a composite, the time to first component event will be used, regardless of other events occurring earlier (e.g., if a stroke precedes an MI in a patient, then the stroke counts in the composite MACE as the first event, but the MI counts in the time to first MI analysis).

4.1.6 Vital status and follow-up of endpoints

Potential endpoints will be collected from randomisation throughout the study until and including the patient's last visit. The investigator will attempt to collect vital status (dead or alive) at the end of the study for all patients, including vital status from publicly available sources for patients who have withdrawn consent, in compliance with local privacy laws/practices.

Known vital status at the end of the study will be defined when the patient is dead or is known to be alive at close-out visit (derived from the eCRF final status form). In patient disposition the number of patients who are dead, alive or with unknown vital status will be reported. The

term lost to follow-up (LTFU) will be limited to only patients with unknown vital status, who did not withdraw consent.

Follow-up of efficacy endpoints will be defined in terms of completion of the event assessment. Thus, a patient that is not LTFU, i.e., with known vital status, may have incomplete follow-up of endpoints.

Complete follow up of the composite of HHF or CV death will be defined as the patient had a HHF or CV death event or had complete event assessment on the individual closing visit.

In addition to the number and percent of patients with complete follow-up, the proportion of total patient time with complete follow-up will be reported per treatment group.

Patient time with complete follow-up will be defined as time from randomisation until the earliest of first primary endpoint event, WoC, censoring due to incomplete event assessment (in cases where last complete event assessment is prior to their individual closing visit) or their individual closing visit. The denominator, representing maximum complete follow-up, will be the time to first HHF or CV death event or patient's individual closing visit.

The Executive Committee will monitor the accrual of patients and when the required number of patients are predicted to have been recruited, upon confirmation from the Sponsor, will instruct all sites that to perform all individual study closure visits by a certain defined date.

4.1.7 Cox Proportional Hazards Model

Cox proportional hazards model will be used to analyse the time-to-events variables. The model will be stratified by country, with treatment as a model term.

With respect to randomised treatment, hazard ratio estimates and 2-sided 95% confidence intervals (CIs) will be presented. No hazard ratio estimates will be given for subgroups with less than 15 events in total, both arms combined. P-values will be presented from the Wald's test.

4.1.8 Analysis of repeated measures

Repeated measure analysis (using PROC MIXED model in SAS) will be used to analyse change from baseline to each relevant time point. The model contains terms for randomised treatment group, baseline measurement, time (each relevant visit) and time by randomised treatment group interaction, and country.

The MIXED model will present least squares (LS) mean estimates and 2-sided 95% confidence intervals (CIs) for treatment difference as well as change from baseline within treatments.

To model the covariance structure, the within patients unstructured covariance structure will be used. The MIXED model is computationally intensive, if the algorithm does not converge, the Toeplitz first-order autoregressive or compound symmetric covariance structure will be used.

4.1.9 Analysis of proportions

Proportions of patients may be analysed using the Cochran-Mantel-Haenszel test, stratified by country. p-value of the test of general association will be presented. Mantel-Haenszel common risk difference will be obtained along with 95% confidence intervals, based on the Sato variance estimator.

4.2 Analysis methods

4.2.1 Patient disposition, demographics and baseline characteristics

The number and percent of patients who completed the study, discontinued from the study will be summarized by treatment group and overall, for all randomised patients. Listings of patients who prematurely discontinued from the study will be provided.

The number and percent of patients who discontinued randomised treatment and reasons for discontinuation of treatment will be summarized by treatment group and overall, for all randomised patients. Listings of patients who prematurely and permanently discontinued treatment will be provided.

Demographic and baseline (as defined in Section 4.1 General principles) characteristics, including medical/disease history, will be summarized, using frequency distributions and summary statistics based on the FAS data set, for each treatment group as well as for all patients combined. No statistical test will be performed for comparison of any baseline measurement among treatment groups.

All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentage will be calculated out of the total number of patients with non-missing observations, overall and by treatment group.

4.2.2 Concomitant and baseline medication

Baseline medications are defined at the index MI hospitalisation discharge visit.

Concomitant medication is defined as medications taken post the index MI event hospitalisation, irrespective of study drug, but will be limited to relevant concomitant cardiovascular medication and treatment for T2DM.

The frequency of baseline and concomitant medications will be presented for the FAS per treatment group.

Summaries of prohibited medication will be presented. In this study prohibited concomitant medication is limited to open label SGLT2 inhibitors taken at any time during the study, at the same time as study drug.

4.2.3 Analysis of the primary efficacy variable and the key secondary endpoint

The objective of the study is to assess clinical benefit. The clinical benefit will be assessed using a hierarchical composite endpoint (HCE) and analysed with the win-ratio method (Pocock et al 2012). The hierarchical assessment will consist of the following endpoints in the following order: death, heart failure events, non-fatal MI, atrial fibrillation/flutter event, new onset of T2DM, NYHA class at last visit and body weight loss at least 5% at last visit. Each patient will be represented by their most severe event within each pair-wise comparison. The pair-wise comparisons will be restricted to the shared follow-up time within each individual pair.

- Compares each patient in the treatment group with each patient in the control group to determine the winner/loser/tie within each pair across the multiple outcomes
- Each paired comparison starts with the most important outcome, and moves to lower priority outcomes only if higher priority outcomes result in a tie
- The win-ratio is the number of wins in the treatment group divided by the number of wins in the control group

CV death will be considered as most severe, followed by non-CV death. If two patients within the same category (for example CV death) are compared, then the patient with shortest time to

event will be considered as more severe. For death and heart failure, adjudicated events will be considered first, followed by investigator reported events (for heart failure). If a patient experienced a heart failure event this patient will be represented by this event, if the patient is not already represented by a death event. Adjudicated heart failure is considered as more severe as compared to Investigator reported. If two patients within the same heart failure category are compared, then shortest time to first event will be considered as more severe. Next step is non-fatal MI. If a patient experienced a non-fatal MI this patient will be represented by this event, if the patient is not already represented by a death event or a heart failure event. Next step is atrial fibrillation/flutter followed by new onset of T2DM. The shortest time to event will be considered also for non-fatal MI, AF/Flutter and T2DM in the same manner as described for death and heart failure. The following step is NYHA at last measurement and at this step all patients will participate (if no event for the first 5 endpoints in the hierarchy). For NYHA class, a significant number of ties are expected, as most patients will have 0 or I which can be considered as the reference, and predominantly patients with NYHA class II, III and IV will affect the analysis. For ties in the NYHA comparison, body weight loss at least 5% at last measurement will be used to break the ties. Note that the first 5 endpoints included in the hierarchical assessment is severe events and that a higher NYHA class is worse than a lower NYHA class (class 0 and I will be combined), while body weight loss at least 5% is beneficial and a patient with at least 5% body weight loss will win against a patient without the loss, in that comparison, if patients have tie for NYHA class and no event for the first 5 endpoints in the hierarchy.

4.2.4 Analysis of the composite of HHF or CV death

This secondary variable is the time to first event included in the composite endpoint. The analysis will be based on the ITT principle using the FAS, including events with onset on or prior to each patient's individual closing visit, adjudicated and confirmed by the CEC committee.

In the analysis of this composite endpoint, treatments (dapagliflozin versus placebo) will be compared using a Cox proportional hazards model with a factor for treatment group, stratified by country using the Efron method for ties. P-values and 95% confidence intervals for the HR will be based on the Wald statistic. The KM rates, p-value, HR, and 95% confidence interval will be reported.

The contribution of each component of this composite endpoint to the overall treatment effect will be examined. In the analysis of the components, all first event of the given type will be included irrespective of any preceding non-fatal composite event of a different type. Consequently, the sum of the number of patients with events in the component analysis will be larger than the number of patients with composite events. Methods similar to those

described for this analysis will be used to separately analyse the time from randomisation to the first occurrence of each of the components.

Kaplan-Meier estimates of the cumulative proportion of patients with event will be calculated and plotted, for the composite endpoint and for the individual components.

HRs and CIs for overall analysis will be presented with forest plots.

The assumption of proportional hazards for the factor for treatment groups will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses.

4.2.5 Subgroup analysis

Exploratory subgroup analyses for the primary composite endpoint as well as for the key secondary endpoint and the composite endpoint of CV death or HHF will be performed for the variables listed in Table 1.

Win-ratio endpoints:

Descriptive statistics will be presented stratified by each subgroup categories including sample size, win ratio with 95% confidence interval, the interaction p-value between treatment effect and subgroup. The interaction p-values are obtained from the hypothesis testing for different treatment benefit across different strata of subgroup variables based on the point estimate and standard error of the natural logarithm of the win ratio. The p-values for interaction will not be adjusted for multiple comparison as the tests are exploratory and will be interpreted descriptively.

The composite of HHF or CV death:

A test of interaction between randomised treatment group and the subgroup variable will be performed in each Cox model, including the relevant subgroup variable and the interaction between treatment and the subgroup variable. In addition to the number and percent of patients with event, KM rate estimate and HR with 95% confidence interval for each subgroup, the interaction p-value will be presented. HRs with confidence interval will be presented in a forest plot, also including the KM rate and interaction p-value. The p-values for interaction will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively.

No hazard ratio estimates with confidence interval and p-values will be given for subgroups with less than 15 events in total, both treatment groups combined.

Table 1 Characteristics and categories for subgroup analysis

Characteristic	**Categories**
Country	Sweden/UK (and subcategorised by Scotland and Wales)
Age (years)	<= 65, >65
Sex	Male, Female
Race	White, Black, or African American, Asian, Other
Medications at baseline (Acetylsalicylic Acid, Statins, ACE Inhibitor/ARB, Thienopyridine/Ticagrelor, Oral Anticoagulants, Beta blockers, Anti-hyperglycemic agents, Aldosterone receptor blocker, Any Antiplatelets)	Yes, No
Baseline Body weight (kg)	<90, ≥90
Baseline BMI (kg/m2)	<30, ≥30
Baseline eGFR by CKD-EPI (ml/min/1.73m^2)	<60, ≥60 <90, ≥90
Baseline DBP and SBP (mmHg)	<80, ≥80 for DBP <130, ≥130 for SBP
Baseline LVEF	<30, 30-49, ≥50
MI index event	STEMI, NSTEMI
Smoking	Yes, No
Previous MI	Yes, No
Previous hypertension	Yes, No
Previous PCI	Yes, No
Previous CABG	Yes, No
Previous Stroke	Yes, No
Previous HF	Yes, No
Baseline HbA1c, Troponin, Creatinine, Glucose	<Median, ≥Median

4.2.6 Sensitivity analysis

Win-ratio endpoints:

A supplementary analysis not taking shared follow-up time into account and excluding pair-wise comparisons where at least one patient has missing data on NYHA class (and no previous events in the hierarchy) and excluding pair-wise comparisons having tie for NYHA class and where at least one patient has missing data on body weight (and no previous events in the hierarchy) may be performed.

The composite of HHF and CV death:

Undetermined cause of death

A sensitivity analysis where deaths adjudicated as 'undetermined' cause are not included as endpoint events, but treated as censoring events, will be performed.

Missing data and informative censoring

The time-to-event analysis using the Cox regression depends on the assumption of non-informative or ignorable censoring, corresponding to the missing-at-random assumption. The missing data in this context are patients who are prematurely censored due to WoC, LTFU or otherwise incomplete follow-up of endpoints. The amount of missing data may be described e.g., in terms of the number of patients and patient time with incomplete follow-up as described in Section 4.1.6.

Patient retention and follow-up are at the forefront of study planning and conduct, and the amount of incomplete follow-up is expected to be small. To assess the impact of missing data and the robustness of the results with regard to the assumption of non-informative censoring, sensitivity analysis will be planned based on the evaluation of the missing follow-up and discussed in relation to the observed efficacy signal. This may include analysis where data for patients with incomplete information related to this endpoint will be imputed using data from patients with complete information.

Incomplete dates

The number of patients with incomplete dates, and the type of incompleteness, will be investigated by randomised treatment arm. If the proportions and degrees of missing are substantially different between treatment arms, the following sensitivity analyses will be considered: 1) Exclude patients who do not have adjudicated date of events and 2) Use multiple imputation to impute dates to account for more uncertainty. For example, for patients who have the year information but not the month and date, randomly select multiple imputed dates in the year interval and average all estimates across imputed datasets.

Investigator reported events

A sensitivity analysis using investigator reported events instead of adjudicated events will be performed.

COVID-19

A sensitivity analysis censoring all patients at any COVID-19-related AEs (defined as any COVID-19-related MedDRA terms) or PDs. The associated estimand strategy regarding intercurrent events will be Hypothetical Strategy (censoring at COVID-19-related AEs or PDs) combined with Treatment Policy (other intercurrent events will be ignored).

Modified Hicks-criteria

The primary approach for HHF adjudication is that it needs to fulfil at least four out of five Hicks-criteria with 1, 2 and 5 being mandatory:

1 The patient is admitted to the hospital with a primary diagnosis of HF.
2 The patient's length-of-stay in hospital extends for at least 24 hours.
3 The patient exhibits documented new or worsening symptoms due to HF.
4 The patient has objective evidence of new or worsening Hf, consisting of at least two physical examination findings or one physical examination finding and at least one laboratory criterion.
5 The patient receives initiation or intensification of treatment specifically for HF.

To assess the robustness of the Hicks-criteria a sensitivity analysis including HHF events fulfilling all five Hicks-criteria instead of the current at least four out of five will be performed.

4.2.7 Analysis of other secondary efficacy variables

The other secondary time-to-event variables will be analysed in a similar manner as for the composite of CV death or HHF. Censoring is described in Section 3. Using MI, stroke, T2DM and hospitalisation for any cause as reported by the investigators and HHF and CV death as adjudicated and confirmed by the CEC.

The change from baseline to last visit (last visit with body weight measurement available after the index hospitalisation) in body weight will be analysed by a repeated measures method

following the method in Section 8. The model will be used to derive a least-squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided nominal p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. Summaries by visit be presented.

4.2.8 CCI

4.2.9 Analysis of recurrent HF events and CV death

The composite outcome of recurrent HF hospitalisations or CV death will be analysed by the semi-parametric proportional rates model (**Lin et al 2000**) known as the LWYY (Lin-Wei-Yang-Ying) method, to test the treatment effect and to quantify the treatment difference in terms of the rate ratio with 95% confidence interval and p-value. Recurrent HF hospitalisations, CV death and censoring processes all have continuous distributions so that HF hospitalisation and death cannot happen at the same time. If a HF hospitalisation and CV death occurred at the same day, then only CV death will be counted. Moreover, CV death is a terminating event which, unlike censoring, prevents the occurrence of new HF hospitalisations.

In addition, the two components in the composite endpoint (total HF hospitalisations and CV death) will be analysed separately to quantify the respective treatment effects and check the consistency between the composite and the components. Total HF hospitalisation will be analysed from the LWYY model and CV death as an individual component from the Cox proportional hazard model Section 4.1.7. For the analysis of total HF hospitalisations component, occurrence of CV death can be regarded as semi-competing risk (informative censoring) and may introduce a bias in the treatment effect estimate for HF hospitalisations (dilution of effect size if the drug has a positive effect on both components).

4.2.10 Analysis of change from baseline

These analyses will be done for the on-treatment period and will include measurements on or after first dose of randomised study drug and on or before 30 days after last dose of study drug.

Change from baseline for HbA1c, diastolic blood pressure (DBP), systolic blood pressure (SBP) and BMI will be analysed by a repeated measures method following the method in Section 4.1.8. The model will be used to derive a least-squares estimate of the treatment difference with 95% confidence interval and corresponding two-sided nominal p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated. Missing data will not be imputed. Summaries by visit be presented.

4.2.11 Analysis of proportions

Preventing symptoms of HF as measured by New York Heart association (NYHA) functional class will be analysed as proportion (of patients having class II or worse at last assessment) as described in Section 4.1.9.

Preventing symptoms of angina as measured by Canadian Cardiovascular Society (CCS) Angina class will be analysed as proportion (of patients having class II or worse at last assessment) as described in Section 4.1.9.

Change in body weight will be analysed as proportion (of patients having at least 5% decrease from baseline to last assessment) as described in Section 4.1.9.

These analyses will include all subjects and all data, and regardless of treatment discontinuation.

4.2.12 Analysis of safety variables

Analysis set

For safety analyses, all summaries will be based on the safety analysis set.

Exposure

The total exposure to study drug will be defined as the length of period on study drug, calculated for each patient as date of last dose – date of first dose +1.

Exposure will be presented descriptively.

Treatment periods

The summaries for the on-treatment period will include events with an onset date on or after first dose of randomised study drug and on or before 30 days after last dose of study drug. Additional presentations will include all events with onset on or after first dose of study drug regardless of whether patients are on or off study treatment at the time of the event (the ‘on +off ‘ treatment period).

All summaries of reportable Aes will be presented for the on-treatment period and the on+off treatment period. The on-treatment period will be the primary analysis approach for all SAEs.

4.2.12.1 Adverse events

See section below

4.2.12.2 Serious adverse events

In Sweden only Aes leading to hospitalisation or death will be collected. In UK all SAEs will be collected.

Collected Aes will be presented as described below both on treatment and on+off treatment.

The number and percent of patients with SAEs will be presented by system organ class (SOC), preferred term (PT) and treatment group. The most common SAEs will also be presented by PT and treatment group only.

SAEs with outcome of death will be presented separately by SOC and PT.

4.2.12.3 Adverse events leading to discontinuation, interruption or dose reduction

Not collected according to CSP.

4.2.12.4 Adverse events of special interest

NA

4.2.12.5 Laboratory Evaluation and vital signs

Summaries of HbA1c, DBP, SBP, Body weight and BMI will be presented in SI units.

The result and the change from baseline will be summarized by treatment group at each scheduled visit using descriptive statistics, including n, mean, SD, median and quartiles.

4.2.12.6 Marked laboratory abnormalities

NA

4.2.12.7 Aes related to COVID-19

All Aes related to COVID-19 will be summarised by randomised treatment group. These Aes will be identified using MedDRA terms.

4.2.13 EQ-5D-5L

To collect utilities assessed by the Euro Quality of Life-5 Dimensions questionnaire (EQ-5D) to support health technology assessment and health economic modelling. A descriptive summary will be presented in the study report. Only data on or after date of randomisation and on or before the date of each patient's individual closing visit will be considered. Further assessments will be analysed and reported separately from the study report. EQ-5D is collected via the Unify app.

4.2.14 Unify app

Assessments of the Unify app will be analysed and reported separately from the study report.

4.2.15 Clever Cap

The number of times during the study that each patient opens (on or after date of randomisation and on or before the date of each patient's individual closing visit) the Clever Cap, will be summarized and presented in the study report. Further assessments will be analysed and reported separately from the study report.

5 INTERIM ANALYSES

Not Applicable

6 CHANGES OF ANALYSIS FROM PROTOCOL

Added the objective/secondary composite endpoint of CV death, HHF or MI.

7 REFERENCES

Kaplan EL and Meier P 1958
Kaplan EL and Meier P. Nonparametric Estimation From Incomplete Observations. Journal of the American Statistical Association 1958;53:457-481.

Robert T. O'Neill, PhD 1997
Secondary Endpoints Cannot Be Validly Analyzed if the Primary Endpoint Does Not Demonstrate Clear Statistical Significance
Controlled Clinical Trials 18:550-556 (1997)

Lin et al 2000
Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 2000; 62(4):711–730.

Pocock et al 2012
Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012 Jan;33(2):176-82. doi: 10.1093/eurheartj/ehr352. Epub 2011 Sep 6. PMID: 21900289.

Yu et al 2022
Yu RX, Ganju J. Sample size formula for a win ratio endpoint. Stat Med. 2022 Mar 15;41(6):950-963. doi: 10.1002/sim.9297. Epub 2022 Jan 27. PMID: 35084052.

8 APPENDIX

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d169dc00001-sap-ed-4		
Document Title:	Statistical Analysis Plan Edition 4	
Document ID:	Doc ID-004228830	
Version Label:	5.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
22-Jun-2023 10:13 UTC	PPD [redacted]	Content Approval
22-Jun-2023 08:00 UTC	PPD [redacted]	Author Approval

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