1. Title Page

Title	Semaglutide in patients with overweight or obesity and heart failure with reduced ejection fraction: safety and effectiveness
Research question & Objectives	To establish the efficacy and safety of semaglutide (GLP-1 RA) in patients with HFrEF and overweight or obesity.
Protocol version	1.0 SwedeHF
Last update date	7 August 2026
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Study registration	**Site:** HMA-EMA catalogue of RWD studies (https://catalogues.ema.europa.eu/node/4713/administrative-details) **Identifier:** EUPAS1000000809
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Conflict of interest	None

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2. Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are currently not recommended by the European and American guidelines to reduce heart failure (HF) events in patients with HF.[1-3] Nevertheless, this drug class is well established in the management of type 2 diabetes and has been shown to reduce cardiovascular (CV) events and HF hospitalisations in these patients, supporting treatment recommendations for patients with diabetes who have, or are at high risk of, atherosclerotic CV disease.[4,5]

Patients with HF with preserved ejection fraction (i.e. left ventricular ejection fraction [LVEF] ≥ 50%; HFpEF) showed a decreased risk of the composite endpoint of CV death and worsening HF (WHF, i.e. HF hospitalisation or urgent out-patient visit due to HF) when treated with the GLP-1 RA semaglutide compared with placebo.[6] In contrast, safety concerns have been raised for patients with HF with reduced ejection fraction (i.e. LVEF ≤ 40%; HFrEF), largely based on a meta-analyses of the EXSCEL, FIGHT, SELECT, FLOW, and HARMONY trials, which suggested an increased risk of WHF in GLP-1 RA users versus placebo.[7,8] Overall, both efficacy and safety of semaglutide in HFrEF remain underexplored and are based on post-hoc analyses of trials or observational data, with limited power and uncertain validity of the HFrEF diagnosis.[9-13]

To the best of our knowledge, the investigator-initiated randomised controlled trial FIT-HF (NCT06423599) is the only ongoing study in patients with HFrEF. However, this trial is not powered to investigate clinical safety outcomes; it primarily compares peak oxygen uptake between semaglutide users and a calorie-restricted diet comparator arm. Expanding the evidence base using high-quality observational data and a target trial emulation (TTE) approach would therefore be valuable and could inform future outcome trials. The relevance of TTE is emphasised by a recently published TTE on GLP-1 RA, based on US healthcare insurance claims data, which replicates and compares the STEP-HFpEF DM and SUMMIT trials.[14] Consequently, the objectives of the present study are to 1) establish the efficacy of GLP-1 RA in overweight and obese patients with HFrEF and 2) to investigate the safety of GLP-1 RA use in these patients, with the aim of excluding clinically relevant adverse effects on key safety endpoints.

The protocol for this observational study has been developed within the TTE framework. The final protocol for the hypothetical target trial is provided in Appendix A.

3. Amendments and updates

Table 1. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
7 August 2026	1.0	-	-	-

4. Milestones

Table 2. Milestones and deliverables

Milestone	Date
Final protocol (SwedeHF version)	August 2026
Data extraction	July/August 2026
Data curation including cohort selection	September 2026
Data analysis	September 2026
First draft	October/November 2026

5. Rationale and background

What is known about the condition: While the metabolic-obese phenotype of HFpEF has a strong rationale for the use of GLP-1 RA, i.e. to reduce visceral and epicardial fat tissue and thus inflammation as well as to optimise glucose and lipid metabolism, less is known about its potential benefit in HFrEF. Concerns have been raised about an increased risk for worsening HF events in this entity, but the underlying evidence is solely of hypothesis-generating character. The increased heart rate in GLP-1 RA users may be a potential mechanism of harm, as sympathetic activation is one of HFrEF's underlying pathophysiologies. On the other hand, obesity is highly prevalent also in HFrEF and may constitute an indication for GLP-1 RA use also in these patients solely based on the obesity indication. Thus, especially GLP-1 RA safety in the context of HFrEF needs to be assessed further.

What is known about the exposure of interest: The active ingredient of interest, semaglutide, was first approved for use in the treatment of type 2 diabetes (Ozempic [subcutaneous], Rybelsus [oral]) and later received approvals of indications for chronic weight management (Wegovy [subcutaneous]) and more recently, cardiovascular risk reduction (Wegovy). Details of the current European Medicines Agency (EMA)-approved indications are provided in Appendix B. Given the potential differences in bioavailability and pharmacokinetics between the subcutaneous and oral formulations, only the subcutaneous will be studied.15

Gaps in knowledge: The safety and consequently the benefit/risk balance in the population of patients with overweight or obesity and HFrEF remains uncertain.

What is the expected contribution of this study? It is expected that this study will provide further supportive evidence on the effectiveness and safety of semaglutide in patients with comorbid conditions of overweight and obesity and HFrEF, which may support an update to the clinical guidelines.

6. Research question and objectives

Table 3. Primary, secondary and exploratory research questions and objectives

A. Co-primary research question and objective (efficacy)

Objective:	To demonstrate that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is superior to SoC in terms of **HF hospitalisation or CV death** in patients with HFrEF and overweight or obesity
Hypothesis:	The use of GLP1-RA is superior in patients in terms of time to HF hospitalisation or CV death
Population:	Patients with overweight (body mass index [BMI] ≥ 27 kg/m2) or obesity (BMI ≥ 30 kg/m2) and HFrEF (LVEF < 40%) and type 2 diabetes
Exposure and treatment strategy:	GLP-1 RA subcutaneous semaglutide as defined in Table 6 plus SoC. The first semaglutide prescription is to be received within 90 days of eligibility
Comparator:	SoC allowing for HF therapy and any dietary or lifestyle advice
Outcome:	Composite of time to first HF hospitalisation or CV death
Time (when follow up begins and ends):	From the date at which the participant meets all criteria to allow inclusion into the study to the date of the event, competing risk of non-CV death, or database cut-off Also see intercurrent events and strategies below
Main measure of effect:	Hazard ratio
Intercurrent events and strategies:	Treatment discontinuation: Treatment policy Switch to oral semaglutide formulation after first subcutaneous prescription (treatment arm): Hypothetical Receiving semaglutide after grace period (control arm): Hypothetical Receiving a non-semaglutide GLP-1 RA treatment: Hypothetical Change in HF therapy: Treatment policy Change in diabetes therapy (excluding GLP-1 RA): Treatment policy Non-CV death: Competing risk, patient to be removed from the “at-risk” set

B. Co-Primary research question and objective (safety)

Objective:	To establish that treatment with the GLP-1 RA semaglutide plus SoC is sufficiently safe in terms of **all-cause hospitalisations or death** compared with SoC in patients with HFrEF and overweight or obesity
Hypothesis:	The use of GLP-1 RA is not detrimental by a clinically meaningful HR threshold of 1.2
Population:	As defined for A
Exposure and treatment strategy:	As defined for A
Comparator:	As defined for A
Outcome:	Time to first all-cause hospitalisation or all-cause death
Time *(when follow up begins and ends):*	From the date at which the participant meets all criteria to allow inclusion into the study to the date of the event or database cut-off Also see intercurrent events and strategies below
Main measure of effect:	Hazard ratio
Intercurrent events and strategies:	Treatment discontinuation: Treatment policy Switch to oral semaglutide formulation after first subcutaneous prescription (treatment arm): Hypothetical Receiving semaglutide after grace period (control arm): Hypothetical Receiving a non-semaglutide GLP-1 RA treatment: Hypothetical Change in HF therapy: Treatment policy Change in diabetes therapy (excluding GLP-1 RA): Treatment policy

C. Secondary research question 1 and objective (efficacy)

Objective:	To demonstrate that treatment with the GLP-1 RA semaglutide plus SoC is superior to SoC in terms of **CV death** in patients with HFrEF and overweight or obesity
Hypothesis:	The use of GLP-1 RA is superior in patients in terms of time to CV death
Population*:*	As defined for A
Exposure and treatment strategy:	As defined for A
Comparator:	As defined for A

Outcome:	Time to CV death
Time *(when follow up begins and ends):*	From the date at which the participant meets all criteria to allow inclusion into the study to the date of the event, competing risk of non-CV death, or database cut-off Also see intercurrent events and strategies below.
Main measure of effect:	Hazard ratio
Intercurrent events and strategies:	Treatment discontinuation: Treatment policy Switch to oral semaglutide formulation after first subcutaneous prescription (treatment arm): Hypothetical Receiving semaglutide after grace period (control arm): Hypothetical Receiving a non-semaglutide GLP-1 RA treatment: Hypothetical Change in HF therapy: Treatment policy Change in diabetes therapy (excluding GLP-1 RA): Treatment policy Non-CV death: Competing risk, patient to be removed from the "at-risk" set

D. Secondary research question 2 and objective (efficacy)

Objective:	To demonstrate that treatment with the GLP-1 RA semaglutide plus SoC is superior to SoC in terms of time to first **HF hospitalisation** in patients with HFrEF and overweight or obesity
Hypothesis:	The use of GLP-1 RA is superior in patients in terms of time to first HF hospitalisation.
Population*:*	As defined for A
Exposure and treatment strategy:	As defined for A
Comparator:	As defined for A
Outcome:	Time to first HF hospitalisation
Time *(when follow up begins and ends):*	From the date at which the participant meets all criteria to allow inclusion into the study to the date of the event, competing risk of any death, or database cut-off Also see intercurrent events and strategies below
Main measure of effect:	Hazard ratio
Intercurrent events and strategies:	Treatment discontinuation: Treatment policy

	Switch to oral semaglutide formulation after first subcutaneous prescription (treatment arm): Hypothetical Receiving semaglutide after grace period (control arm): Hypothetical Receiving a non-semaglutide GLP-1 RA treatment: Hypothetical Change in HF therapy: Treatment policy Change in diabetes therapy (excluding GLP-1 RA): Treatment policy Death: Competing risk, patient to be removed from the "at-risk" set

E. Secondary research question 2 and objective (safety)

Objective:	To establish that treatment with the GLP-1 RA semaglutide plus SoC is sufficiently safe in terms of **all-cause death** compared with SoC in patients with HFrEF and obesity
Hypothesis:	The use of GLP-1 RA is not detrimental by a clinically meaningful HR threshold of 1.2
Population*:*	As defined for A
Exposure and treatment strategy:	As defined for A
Comparator:	As defined for A
Outcome:	Time to all-cause death
Time *(when follow up begins and ends):*	From the date at which the participant meets all criteria to allow inclusion into the study to the date of the event or database cut-off Also see intercurrent events and strategies below
Main measure of effect:	Hazard ratio
Intercurrent events and strategies:	Treatment discontinuation: Treatment policy Switch to oral semaglutide formulation after first subcutaneous prescription (treatment arm): Hypothetical Receiving semaglutide after grace period (control arm): Hypothetical Receiving a non-semaglutide GLP-1 RA treatment: Hypothetical Change in HF therapy: Treatment policy Change in diabetes therapy (excluding GLP-1 RA): Treatment policy

F. Secondary research question 2 and objective (safety)

Objective:	To establish that treatment with the GLP-1 RA semaglutide plus SoC is sufficiently safe in terms of **all-cause hospitalisation** compared with SoC in patients with HFrEF and obesity
Hypothesis:	The use of GLP-1 RA is not detrimental by a clinically meaningful HR threshold of 1.2
Population*:*	As defined for A
Exposure and treatment strategy:	As defined for A
Comparator:	As defined for A
Outcome:	Time to all-cause hospitalisation
Time *(when follow up begins and ends):*	From the date at which the participant meets all criteria to allow inclusion into the study to the date of the event, competing risk of death, or database cut-off Also see intercurrent events and strategies below
Main measure of effect:	Hazard ratio
Intercurrent events and strategies:	Treatment discontinuation: Treatment policy Switch to oral semaglutide formulation after first subcutaneous prescription (treatment arm): Hypothetical GLP-1 RA treatment switch/crossover (for control arm): Hypothetical Change in HF therapy: Treatment policy Change in diabetes therapy: Treatment policy Death: Competing risk, patient to be removed from the “at-risk” set

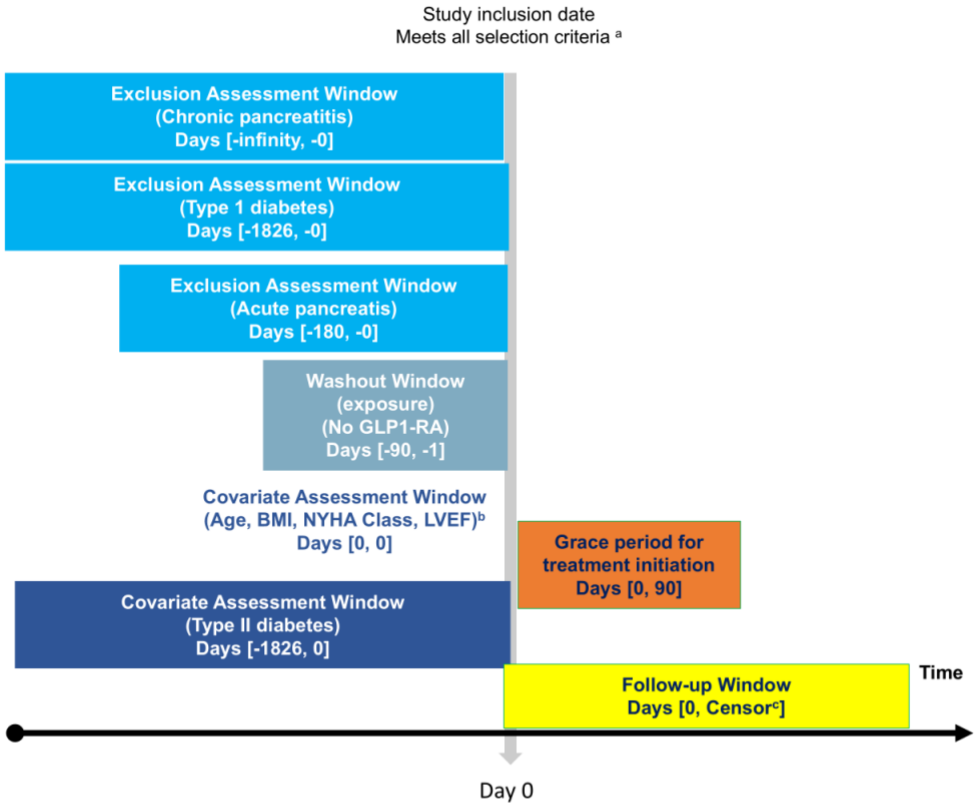
7. Research methods

7.1. Study design

Research design: registry-based cohort study using the TTE framework.

Rationale for study design choice: There is currently no RCT ongoing or planned and it is unlikely that one will be initiated. The TTE framework is a systematic approach to design an observational study with the goal to reduce potential biases.

7.2. Study design diagram



Note: the screening of patient records in the registry will start from the first recorded date of any semaglutide prescription in the registry, regardless of other eligibility criteria

a. The full list of inclusion and exclusion criteria are provided in Tables 4 and 5
b. Age ≥ 18 years, BMI ≥ 27 kg/m2, NYHA class II-IV, LVEF < 40%
c. Follow up until date of event, date of relevant intercurrent event or administrative censoring of registry data

Figure 1. Representation of study design aspects with respect to the study inclusion date (day 0)

7.3. Setting

7.3.1. Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

Cohort eligibility period: start date

The first marketing authorisation for semaglutide as an active ingredient was issued by the European Commission on 8 February 2018 for Ozempic, however the market access date in Sweden has not been publicly disclosed. This means that we do not know the exact date for which semaglutide was first available to patients. For this reason, the study start date will be based on the date of the first recorded subcutaneous semaglutide prescription in the Swedish registry, regardless of whether it was prescribed for a patient that would have been eligible for entry into the cohort.

Entry into the study cohort: individuals

Entry into the study cohort will be allowed when a patient meets all inclusion criteria without any exclusion criteria (see

Table 4 and Table 5).

It is possible that multiple screening moments (i.e. multiple records) for each patient are available in the SwedeHF registry. A patient is only able to be "successfully screened" for entry into the cohort once. The date at which this occurs will be the patient's time 0 and from that time they will be at risk of experiencing an event.

The full set of patient records that are available after the start of the cohort eligibility period can be used in chronological order for screening into the study.

End date: cohort

The administrative censoring of the registry data is December 31, 2024. Follow-up for specific endpoints will depend on the event of interest and the intercurrent events.

7.3.2. Context and rationale for study inclusion criteria

The restriction to ≥ 18 years of age is in line with the target population.

In the hypothetical target trial protocol, we had decided to require a BMI of at least 30 kg/m2 as this is the expected group of patients with HFrEF that would be most likely to receive GLP-1 RA without any further comorbidities. For the emulation study, we have decided to expand to patients that also have a BMI between 27 kg/m2 and 30 kg/m2. This was largely a pragmatic decision that was needed to ensure sufficient patient numbers in the study, but it is also a relevant research question given that Wegovy is approved for weight management for patients with a BMI between 27 kg/m2 and 30 kg/m2 plus a weight-related comorbidity.

To ensure that patients were eligible to receive all approved semaglutide indications, the inclusion criterion of type 2 diabetes has been added to the inclusion criteria. Ozempic is indicated for the treatment of patients with type 2 diabetes, and for Wegovy overweight patients require at least one weight-related comorbidity, including type 2 diabetes. Without the inclusion criterion of type 2 diabetes, patients with only overweight or obesity would have been eligible to enter the study, but were not eligible to receive Ozempic or Wegovy in the absence of an additional weight-related comorbidity. This would have resulted in the positivity assumption being violated.

While safety concerns for GLP-1 RA use exist primarily in patients with HFrEF, little is known about patients with HF mildly reduced LVEF (HFmrEF), as parts of this entity are usually counted towards either HFpEF or HFrEF in randomised controlled trials: in the landmark trials STEP-HFpEF and STEP-HFpEF DM, only patients with $< 45\%$ LVEF (i.e. including the upper part of the HFmrEF spectrum) were included.16,17 In the SUMMIT trial, only patients with HFpEF as defined by the guidelines (i.e. $\geq$ 50% LVEF) were included.18 For this target trial, we chose to include patients who were not represented in either of the STEP-HFpEF trials – namely, those with an LVEF $< 40\%$.

Table 4. Inclusion criteria for entry into study cohort

Criterion	Definition	Variable label
Age ≥ 18 years	Collected in the SwedeHF CRF.	shf_age
LVEF < 40%	Categorical variable indicating LVEF level. Collected in the SwedeHF CRF; in-patients: status at discharge; out-patients: status after visit. Assumed to be at date of each HF visit/record but could be up to a month earlier.	shf_ef
NYHA class II-IV	Categorical variable indicating NYHA class. Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_nyha
BMI ≥ 27 kg/m2	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_bmi
Type 2 diabetes	Flagged as type 2 diabetes if: a) NPR: ICD-10-SE code E11 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days) OR b) Collected and recorded as type 2 diabetes in the SwedeHF CRF	shf_com_diabetes (only NPR) [Value for Type 2] shf_diabetestype (only SwedeHF) [Value for Type 2] shf_sos_com_diabetes (both NPR and SwedeHF) [Value for Type 2]

Abbreviations: BMI, body mass index; CRF, case report form; HF, heart failure; ICD-10-SE, International Classification of Diseases, 10th revision, Swedish version; LVEF, left ventricular ejection fraction; NPR, National Patient Register; NYHA, New York Heart Association classification; SHFDB5, Swedish Heart Failure Registry, database version 5; SwedeHF, Swedish Heart Failure Registry.

7.3.3. Context and rationale for study exclusion criteria

The exclusion criteria are largely in line with other randomised controlled trials performed in this area. They address important comorbidities, especially those that pose an unjustifiable risk to the patients receiving semaglutide (e.g. known allergy) or would hamper trial interpretation (e.g. prior GLP-1 RA use or low adherence).

Table 5. Operational definitions for exclusion criteria

Criterion	Definition	Variable label
Type 1 diabetes	Flagged as diabetes type 1 if: a) NPR: ICD-10-SE code E10 ((setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days) OR b) Collected and recorded as type 1 diabetes in the SwedeHF CRF.	Variables as for Type 2 diabetes [Value for Type 1]
Current use of a GLP-1 RA or use in the past 180 days	NPDR: ATC code A10BJ (timeframe: -180 to -1 days). For any use of GLP-1 RAs apart from semaglutide, the actual record date (time 0) should also result in exclusion.	To be derived during data curation step
Acute pancreatitis in prior 180 days	NPR: ICD-10-SE code K85 (setting: in- and out-patients; position: all diagnoses; timeframe: -180 – 0 days)	sos_com_acupanc_pr180d (new)
Diagnosis of chronic pancreatitis	NPR: ICD-10-SE code K86.0 or K86.1 (setting: in- and out-patients; position: all diagnoses; timeframe: [year]1997– 0 days)	sos_com_chronpancr (new)

Abbreviations: ATC, anatomic therapeutical drug classification; CRF, case report form; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; ICD-10-SE, International Classification of Diseases, 10th revision, Swedish version; NPDR, National Prescribed Drug Register; NPR, National Patient Register; SHFDB5, Swedish Heart Failure Registry, database version 5; SwedeHF, Swedish Heart Failure Registry.

7.4. Variables

7.4.1. Context and rationale for exposure(s) of interest

The exposure of interest is the subcutaneous formulation of semaglutide, administered according to the label.

The comparator is SoC for HF, diabetes, and lifestyle advice for overweight or obesity. It is also assumed that patients in the semaglutide group also receive SoC, so semaglutide can be seen as an add-on treatment to SoC.

Table 6. Definitions of treatment and comparator groups

	Definition	Comment	Variable label
Treatment group			
SoC for HF, as an add on to diabetes medication and including dietary and lifestyle advice for weight reduction, plus: semaglutide (ATC code A10BJ06), subcutaneous injection once weekly. The target dose is 2.4 mg. Dose escalation schedule: week 1-4, 0.25 mg; week 5-8, 0.5 mg; week 9-12, 1 mg; week 13-16, 1.7 mg; week > 16, 2.4 mg. In case of unacceptable (esp. gastrointestinal) adverse drug reactions, slower up titration, pausing, or lower target dose can be applied.	NPDR: ATC code A10BJ06 (timeframe: 0 – 90 days) Variable route = Parenteral	Titration cannot be assessed in the registries. Treatment strategy: Semaglutide prescribed within 90 days of study entry.	For semaglutide SC first prescription after index without timeframe To be derived during data curation _tmt90gp (= 1) for primary grace period
Comparator group			
SoC for HF, as an add on to diabetes medication and including dietary and lifestyle advice for weight reduction	NPDR: absence of ATC code A10BJ06 (timeframe: 0 – 90 days)	We assume that SoC for HF, diabetes, and overweight/obesity is provided.	_tmt90gp (=0)

Abbreviations: ATC, anatomic therapeutical drug classification; HF, heart failure; NPDR, National Prescribed Drug Register; SHFDB5, Swedish Heart Failure Registry, database version 5.

7.4.2. Context and rationale for outcome(s) of interest

Table 7. Operational definitions of outcomes

Outcome name	Definition	Derivation algorithm	Variable label
1) Time to first HF hospitalisation	NPR: ICD-10-SE codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, K76.1, or R57.0 (setting: in-patients; position: main diagnosis; timeframe: timeframe: 1 – infinite days).	Identify if any HF hospitalisations occurred after study inclusion date. Check if any intercurrent events or deaths have occurred and whether these require censoring. If yes, then flag the relevant intercurrent event or death at this date. If at least one event, and no intercurrent events requiring censoring have occurred, then select the earliest HF hospitalisation after study inclusion date for the outcome. If no event, then select the earliest time of intercurrent event requiring censoring, death, or administrative censoring of the registry data.	To be derived during data curation
2) Time to CV death	CoD: ICD-10-SE codes I, J81, K76.1, R57.0, or G45 (ULORSAK).	Identify if CV death occurred after study inclusion date. Check if any intercurrent events or non-CV deaths have occurred and whether these require censoring. If yes, then flag the relevant intercurrent event or non-CV death at this date. If CV death event, and no intercurrent events requiring censoring have occurred, then use the CV event date. If no CV death, then select the earliest time of intercurrent event requiring censoring,	event: sos_out_deathcv time: sos_outtime_death

		non-CV death, or administrative censoring of the registry data.	
3) Time to first all-cause hospitalisation	NPR: all ICD-10-SE codes (setting: in-patients; position: all diagnoses; timeframe: 1 – infinite days).	As for 1) except based on the event of all-cause hospitalisation	To be derived during data curation
4) Time to all-cause death	CoD: all ICD-10-SE codes (ULORSAK).	As for 2) except based on the event of all-cause death	event: sos_out_death time: sos_outtime_death
Composite endpoints			
Time to first HF hospitalisation or CV death	Combination of 1) and 2) above.	Select the earliest of the two events from 1) and 2) above. If no event, then select the earliest time of intercurrent event requiring censoring, death, or administrative censoring of the registry data..	To be derived during data curation
Time to first all-cause hospitalisation or all-cause death	Combination of 3) and 4) above.	Select the earliest of the two events from 3) and 4) above. If no event, then select the earliest time of intercurrent event requiring censoring, death, or administrative censoring of the registry data.	To be derived during data curation

Abbreviations: CoD, National Cause of Death Register; CV, cardiovascular; HF, heart failure; ICD-10-SE, International Classification of Diseases, 10th revision, Swedish version; NPR, National Patient Register; SHFDB5, Swedish Heart Failure Registry, database version 5; ULORSAK, cause of death (as an ICD-10-SE code).

Table 8. Intercurrent events and competing risks to be collected

Intercurrent event	**Details/comments**	**Variable labels**
Treatment discontinuation (treatment group)	Absence of semaglutide prescription for 180 days after first prescription	N/A

	Treatment policy strategy and difficult to specify so we will not collect	
Receiving semaglutide or any other GLP-1 RA after grace period (control group)	Can be based on GLP-1 RA code and time variables. Includes any GLP-1 RA including semaglutide after grace period. Dependent on grace period definition. NPDR: ATC code A10BJ06	To be derived during data curation
Receiving oral semaglutide at any time	Based on variables that are used to differentiate between subcutaneous and oral semaglutide administration routes for treatment group. Need yes/no and time variables.	To be derived during data curation
Receiving a non-semaglutide GLP-1 RA treatment (treatment group)	ATC code A10BJ (all GLP-1 RA) excl. ATC code A10BJ06 (semaglutide)	To be derived during data curation
Non-CV death	Available in outcomes dataset	sos_out_deathnoncv
Change in HF therapy	Given this relates to changes in background therapy and we are interested in the treatment effect regardless of change in background therapy this variable will not be collected	N/A
Change in diabetes therapy (excluding GLP-1 RA)	Given this relates to changes in background therapy and we are interested in the treatment effect regardless of change in background therapy this variable will not be collected	N/A

7.4.3. Context and rationale for follow-up

The study follow up is based on available records in the NPR and CoD

7.4.4. Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

The main covariates to be identified are those associated with treatment decisions and that will be included in the weighting models as part of the clone-censor-weighting (CCW) approach. These should be associated with the probability of remaining uncensored in each of the groups and/or prognostic of the outcomes. The respective selection of covariates is marked with an * in Table **9**.

Table 9. Operational definitions of covariates

Characteristics	Definition / Comment	Variable label
Sociodemographics		
Age (years), median [IQR]*	Collected in the SwedeHF CRF.	shf_age
Sex*	Collected in the SwedeHF CRF.	shf_sex
- female, n (%)	-	-
- male, n (%)	-	-
Disposable income > median (grouped by year), n (%)	Status on Dec 31 of the year prior to the SwedeHF visit used to determine the study inclusion date. Acquired from the LISA database.	scb_dispincome
Education*	Status on Dec 31 of the year prior to the SwedeHF visit used to determine the study inclusion date. Acquired from the LISA database.	scb_education
- compulsory school, n (%)	-	-
- secondary school, n (%)	-	-
- university, n (%)	-	-
Family status*	Status on Dec 31 of the year prior to the SwedeHF visit used to determine the study inclusion date. Acquired from the LISA database.	scb_famtype
- living alone, n (%)	-	-
- cohabitating, n (%)	-	-
Clinical variables of heart failure and obesity		

Characteristics	Definition / Comment	Variable label
LVEF*	Collected in the SwedeHF CRF; latest recorded LVEF at each visit (not necessarily measured at the time of the visit but possibly before).	shf_ef
- < 30%, n (%)	-	-
- 30-39%, n (%)	-	-
NYHA class*	Collected in the SwedeHF CRF.	shf_nyha
- I, n (%)	-	-
- II, n (%)	-	-
- III, n (%)	-	-
- IV, n (%)	-	-
Duration of HF (days), median [IQR]*	Time from first in-patient discharge or out-patient visit with registration of a HF code in in the NPR to the study inclusion date: ICD-10-SE codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, K76.1, R57.0, or ICD-9-SE codes 414W, 425E, 425F, 425G, 425H, 425W, 425X, or 428 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 days).	sos_durationhf
≥ 1 HF hospitalisation in prior year, n (%)*	Any HF hospitalisation either in the NPR or in SwedeHF. NPR: ICD-10-SE codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.3, I42.5-9, I43, I50, J81, K76.1, or R57.0 (setting: in-patients; position: main diagnosis; timeframe: -365 – 0 days). SwedeHF: any registration with shf_location = In-patient.	shf_sos_prevhfh1yr
BMI (kg/m^2), median [IQR]*	Calculated as weight/height^2, using the respective variables in SwedeHF; if no height had been registered, it was imputed. Weight was captured at discharge from hospital in in-patients; if missing, it was replaced by weight at admission to hospital.	shf_bmi
Comorbidities & cardiovascular risk factors		
Arterial hypertension, n (%)*	NPR: ICD-10-SE codes I10-15 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days).	sos_com_hypertension
Atrial fibrillation/flutter, n (%)	Diagnosis of atrial fibrillation/flutter in the NPR or in SwedeHF. NPR: ICD-10-SE code I48 (setting: in- and out-patients; position: all diagnoses; timeframe: --1,826 – 0 days).	shf_sos_com_af

Characteristics	Definition / Comment	Variable label
	SwedeHF: diagnosis in any registration.	
Valvular disease, n (%)	NPR: ICD-10-SE codes I05-08, I34-39, Q22, Q23.0-3, Q23.8-9, or Z95.2-4 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days).	sos_com_valvular
Ischaemic heart disease, n (%)*	NPR: ICD-10-SE codes I20-25 or ICD-9-SE codes 410-4 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 years).	sos_com_ihd
History of myocardial infarction, n (%)*	NPR: ICD-10-SE codes I21, I22, I25.2, or ICD-9-SE codes 410 or 412 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days).	sos_com_mi
History of sleep apnoea, n (%)*	NPR: ICD-10-SE code G47.3 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days).	sos_com_sleepapnoea
History of hypercholesterinaemia* n(%)	NPR: E78.5, E78.0, E78.1, E78.2, E78.4	sos_com_hyperchol
Dialysis, n (%)*	NPR: ICD-10-SE codes Z49.0-2 or Z99.2 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days), or KVÅ codes DR012, DR013, DR014, DR016, DR020, DR024, TJA33, DR055, DR056, DR060, DR061, or QF006 (timeframe: -1,826 – 0 days).	sos_com_dialysis
COPD, n (%)	NPR: ICD-10-SE codes J40-4 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days).	sos_com_copd
Smoking*	Collected in the SwedeHF CRF.	shf_smoke
- current smoker, n (%)	-	-
- former smoker, n (%)	-	-
- never smoked, n (%)	-	-
Liver disease, n (%)	NPR: ICD-10-SE codes B18, I85, I86.4, I98.2, K70, K71.0, K71.1, K71.3-7, K72-4, K76.0, or K76.2-9 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days).	sos_com_liver
Peripheral artery disease, n (%)*	NPR: ICD-10-SE codes I70-3 (setting: in- and out-patients; position: all diagnoses; timeframe: -1,826 – 0 days).	sos_com_pad
History of stroke, n (%)*	NPR: ICD-10-SE codes I60-4, I69.0-4, or ICD-9-SE codes 430-4 or 438 (setting: in- and out-patients; position: all diagnoses; timeframe: -infinite – 0 days).	sos_com_stroke

Characteristics	Definition / Comment	Variable label
Anaemia, n (%)	Calculated from SwedeHF data: haemoglobin < 120 g/l (women) or < 130 g/l (men).	shf_anemia
Cancer (exceptions: non-melanoma skin cancer, localised prostate cancer), n (%)*	NPR: ICD-10-SE code C (malignant tumours without in-situ) but not C44 (non-melanoma malignant skin cancers) and not C61.9 in the absence of any other C code (localised prostate cancer) (setting: in- and out-patients; position: main diagnosis; timeframe: -1,826 – 0 days).	sos_com_cancer
Charlson Comorbidity Index, median [IQR]*	Calculated as an adapted score for all patients in SwedeHF based on NPR data according to Ludvigsson et al. (in-patients: status at discharge; out-patients: status after visit).	sos_com_charlsonci
Vital signs		
Systolic blood pressure (mmHg), median [IQR]*	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_bpsys
Diastolic blood pressure (mmHg), median [IQR]	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_bpdia
Mean arterial pressure (mmHg), median [IQR]	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_map
Heart rate (bpm), median [IQR]*	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_heartrate
Laboratory parameters		
Haemoglobin (g/l), median [IQR]	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_hb
Potassium (mmol/l), median [IQR]	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_potassium
Sodium (mmol/l), median (IQR)	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_sodium
eGFR (ml/min/1.73 m²), median [IQR]*	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_crea
NT-proBNP (pg/ml), median [IQR]*	Collected in the SwedeHF CRF (if in-patient visit: at discharge if available, otherwise at admission).	shf_ntprobnp

Characteristics	Definition / Comment	Variable label
Cardio-circulatory treatment		
Beta-blocker, n (%)*	Collected in the SwedeHF CRF.	shf_bbl
ACEi / ARB / ARNi, n (%)*	Collected in the SwedeHF CRF.	shf_rasiarni
MRA, n (%)*	Collected in the SwedeHF CRF.	shf_mra
SGLT2i, n (%)*	Collected in the SwedeHF CRF.	shf_sglt2
Diuretic (all), n (%)	Collected in the SwedeHF CRF.	shf_diuretic
Loop diuretic, n (%)*	Collected in the SwedeHF CRF.	shf_loopdiuretic
Digoxin, n (%)	Collected in the SwedeHF CRF.	shf_digoxin
Nitrate, n (%)*	Collected in the SwedeHF CRF.	shf_nitrate
Anticoagulant, n (%)	Collected in the SwedeHF CRF.	shf_anticoagulantia
Platelet inhibitor, n (%)*	Collected in the SwedeHF CRF.	shf_asaantiplatelet
Statin, n (%)*	Collected in the SwedeHF CRF.	shf_statin
Cardiac devices*	Collected in the SwedeHF CRF.	shf_device
- no device, n (%)	-	-
- pacemaker, n (%)	-	-
- CRT-P, n (%)	-	-
- CRT-D, n (%)	-	-
- ICD, n (%)	-	-
Index visit & follow-up		
Year of index visit, median [IQR]*	Collected in the SwedeHF CRF.	shf_indexyear
Location of index visit*	Collected in the SwedeHF CRF.	shf_location

Characteristics	Definition / Comment	Variable label
- in-patient, n (%)	-	-
- out-patient, n (%)	-	-
Planned follow-up setting*	Collected in the SwedeHF CRF.	shf_followuplocation_cat
- primary care, n (%)	-	-
- specialty care, n (%)	-	-
Planned follow-up in a HF nurse clinic, n (%)*	Collected in the SwedeHF CRF.	shf_followuphfunit

Variables collected in SwedeHF represent the status at the end of the index visit (i.e. discharge in in-patients), if not explicitly stated otherwise. **Variables marked with * are considered in the weighting model for treatment allocation. Abbreviations:** ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; bpm, beats per minute; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRF, case report form; CRT-P/D, cardiac resynchronisation therapy pacemaker/defibrillator; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; ICD-10-SE, International Classification of Diseases, 10th revision, Swedish version; ICD-9-SE, International Classification of Diseases, 9th revision, Swedish version; IQR, interquartile range; KVÅ, Klassifikation av vårdåtgärder (procedure codes); LISA, Longitudinal Integrated Database for Health Insurance and Labour Market Studies; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; n (%), total number of patients (relative number of patients); NPR, National Patient Register; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association classification; SGLT2i, sodium/glucose cotransporter 2 inhibitor; SHFDB5, Swedish Heart Failure Registry, database version 5; SwedeHF, Swedish Heart Failure Registry.

7.5. Data analysis

7.5.1. Context and rationale for analysis plan

Given the patients in SwedeHF will not be immediately prescribed a GLP-1 RA, a grace period will be specified for which successfully screened patients are allowed to receive GLP-1 RA under the relevant treatment strategy. For the primary analysis, this will be 90 days. To explore the robustness of the results to the grace period, sensitivity analyses for the grace periods of 60 and 120 days will be performed.

To account for the grace period, and to prevent immortal time bias, the CCW method will be used. This is briefly described below.

Clone

Create two identical copies (clones) of the data. Allocate one copy to the treatment strategy: “Semaglutide prescribed within 90 days of eligibility” and the other to the control strategy: “No semaglutide prescribed within 90 days of eligibility.” By design, the groups are identical at time 0 and all observed and unobserved confounders are balanced.

Censoring for treatment

Patients contribute to the at-risk set until they no longer meet the specified treatment strategy, at which point they are censored. For example, if a patient is prescribed semaglutide within 90 days then they are censored in the control group at the time of semaglutide prescription. If patients have not received semaglutide by day 90 then this is no longer consistent with the defined treatment strategy for semaglutide and are censored from the treatment group at day 90. This censoring is termed “artificial censoring” as it is induced by design.

Prior to artificial censoring, patients remain at risk for events in both groups and if an event occurs then this is recorded as an event in both groups. Censoring for other reasons can also occur during this time.

Weighting to account for artificial censoring

While the groups are balanced at time 0 by design, the artificial censoring is likely to be dependent on other confounding factors.

To retain the balance between the groups, an inverse probability of censoring weighting model is to be fitted, with the probability of remaining uncensored estimated separately for the treatment groups. Given the nature of the registry data, not all patients will have time-varying covariates available. For this reason, only the values of “baseline” covariates at the time each patient is eligible (i.e. time 0) will be included in the weighting model. The covariates to be included in the weighting models are denoted with an * in Table **9**.

For the treatment group, the only time at which patients can be censored is the end of the grace period (i.e. 90 days for the primary analysis), given they remain eligible to receive treatment until that timepoint. Therefore the probability of being uncensored will be estimated using logistic regression.

For the control group, patients can be censored due to receiving treatment at any time from time 0 until the end of the grace period. The probability of remaining censored will be estimated using pooled logistic regression. For this, the data will be converted into a person-period dataset. Week will initially be used to define the discrete time interval. If there are any problems with fitting the models then a 2 week period will be used, followed by month.

Stabilized weights will be calculated by dividing the unconditional probability of remaining uncensored up to time t by the individual’s estimated probability of remaining uncensored.

Diagnostics for IPCW

In order to evaluate the performance of IPCW a number of diagnostics will be performed.

- Covariate balance: Check whether the weighted censoring process is approximately independent of the baseline predictors. Standardized mean differences (SMDs) will be compared before and after IPCW. SMDs < 0.1 will be considered acceptable.
- To evaluate potential for violation of the positivity assumption: Examine the fitted censoring probabilities using descriptives and plots. Very small values may suggest a violation of the positivity assumption.
- To evaluate stability of weights, including over time: Examine the stabilized weights using descriptives and plots, including over time for the control group.

A priori we do not expect problems with the positivity assumption and therefore the primary analysis will be untruncated, a truncated sensitivity analysis will be pre-planned by truncating at 1^{st}/99^{th} percentile and 2.5^{th}/97.5^{th} percentiles.

The CCW approach will be repeated for each of the primary and secondary endpoints.

Censoring for other reasons

For intercurrent events for which the hypothetical strategy is to be applied, follow up times for patients will be censored at the time at which the intercurrent event occurred. In line with current approaches in clinical trials no weighting approaches will be applied.

Administrative censoring will also be present due to the data cut off of the registry. For patients who are event free and not otherwise censored, their follow up times will be censored at the data cut-off date. This assumes that all relevant events would have been captured in the registry.

Descriptive analyses

For all time-to-first-event endpoints, Kaplan-Meier plots for endpoints without (non-CV) death as a competing risk will be presented by treatment arm, and cumulative incidence functions for endpoints with (non-CV) death as a competing risk. The percentage of participants who have experienced an event at 6 months and at each year (1, 2, 3, 4, and 5 years) will be summarised.

A table of characteristics of patients who were included in the study will be produced.

For each outcome, a study flow diagram will be produced to show the flow of eligible patients through cloning, artificial censoring, censoring for other reasons and events. This flow will also identify the number of patients in the treatment group who received Ozempic vs Wegovy.

Estimation and inference

Weighted cox proportional hazards model will be used to estimate the hazard ratio (HR; or a cause-specific HR in the case of analysis involving competing risks) with 95% confidence interval of GLP-1 RA + SoC vs placebo + SoC. For the efficacy endpoint, the p-value associated with the estimation of the (cause-specific) HR will be used for inferences.

All analyses will be performed in R. A list of packages used will be provided as part of the final code.

Approaches to handle missing data

Missing outcome data will not be imputed. For the inclusion and exclusion criteria, relevant time windows have been stated in Table 4 and Table 5. No further missing data approaches will be applied to determine study inclusion.

For the baseline covariates included in the weighting models, if these are incomplete then multiple imputation will be used. Missing data on baseline covariates that are included for descriptive purposes only will not be imputed.

Multiple imputation will be applied prior to the application of IPCW. We will impute 20 incomplete datasets using fully conditional specification. Continuous variables will be imputed using linear regression, binary using logistic regression, an multinomial logistic regression will be used for categorical variables. For each imputed dataset, the IPCW and analysis models will be applied and the final estimates will be combined using Rubin's rules. The imputation models will include all variables to be included in the models to estimate the probability of remaining uncensored.

Upper limit of the HR to rule out meaningful negative effects

For the primary safety endpoint with an objective to demonstrate that the use of semaglutide is not detrimental for patients in terms of safety, under the assumption that there is no difference between the groups (i.e. the HR = 1), an HR threshold of 1.2 will be specified. This means that the upper limit of the 95% confidence interval for the HR must be below 1.2 in order to support a conclusion that the use of semaglutide does not result in a (meaningful) negative effect. All analyses relate to time-to-event outcomes and differ only by whether there is a competing risk of (non-CV) death.

Table 10. Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Sensitivity analysis 1	Length of the grace period. Shortened to 60 days and lengthened to 120 days.	Whether the choice of the grace period has an influence on the results.	Patients are less likely to experience the event of interest by the end of the grace period.	60 days might be too short to allow patients to receive semaglutide. 120 days may not represent a clinically realistic grace period.
Sensitivity analysis 2	Estimator - Restricted Mean Survival Time (RMST) used, tau (time at which RMST is evaluated) is 3 years.	Impact of estimator and proportional hazards assumption in the primary analyses.	Non-proportional hazards assumption is not required.	The time at which the Restricted Mean Survival Time is estimated needs to be pre-specified.
Supplementary estimand 1	Estimand for safety analyses. Hypothetical estimand for	Understand whether conclusions related to safety differ depending on approach	This supplemental estimand approach more closely reflects the	The assumption does not reflect real-world practice.

	patients in the semaglutide arm who stop treatment .	to the intercurrent event of treatment discontinuation.	approach that is used for safety endpoints.

Subgroup analyses

For the two co-primary endpoints, prespecified subgroup analyses will be performed based on physiological reasoning and prior evidence:

- Age (< 50, 50-69, ≥70+ years)
- SGLT2i (yes vs no)
- LVEF (≤30% vs > 30%) (defines severe cardiac dysfunction according to ESC and ACC/AHA/HFSA HF guidelines)
- Sex (male vs female)
- NT-proBNP (≥ 700 ng/l vs < 700 ng/l)
- History of HF hospitalisation (yes vs no)
- NYHA (II vs III/IV)
- BMI (< 35 kg/m2 vs ≥ 35 kg/m2)
- eGFR (< 30, 30-60, > 60 ml/min/1.73m2)

7.6. Data sources

7.6.1. Context and rationale for data sources

The registries below can be linked to each other using the Swedish unique personal identification number.

Strengths of data source(s):

a) Swedish Heart Failure Registry (SwedeHF): leading HF registry in Scandinavia with circa 80 registered variables, 60% coverage of prevalent HF, and linkage to other national registries.

b) Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA): national registry with near to complete coverage of sociodemographic variables and quality assurance.

c) National Patient Registry (NPR): national registry with near to complete coverage of specialist care.

d) National Prescribed Drug Registry (NPDR): national registry with near to complete coverage of prescribed and dispensed medication.

e) National Cause of Death Registry (CoD): national registry with near to complete coverage of cause-specific mortality.

Limitations of data source(s):

a) Swedish Heart Failure Registry (SwedeHF): not full coverage, recruitment in primary care not from the beginning and underrepresented.

b) Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA): not full coverage of some parameters, especially education in immigrants / yearly updates.

c) National Patient Registry (NPR): no data from primary care, information from routine care without adjudication.

d) National Prescribed Drug Registry (NPDR): prescribed and dispensed drugs, but no information on actual use of medication or medication without prescription.

e) National Cause of Death Registry (CoD): causes are reported by physicians in death certificates, not adjudicated.

7.7. Data management

Detailed information on data management is provided and updated regularly on github: https://kiheartfailure.github.io/shfdb5/

7.8. Quality control

Quality assurance is managed within the respective registries.

7.9. Study size and feasibility

The following calculations were made for the target trial protocol:

Efficacy (superiority): Based on available literature, it is expected that the proportion of patients in the comparator arm who have experienced a HF event or a CV-related death by 5 years after randomisation is 30%.[6,20] A HR of 0.8 is considered to be clinically meaningful (meaning that around 25% of patients in the treatment arm would have experienced the event by 5 years). With a two-sided alpha of 0.05 and 90% power, the number of events required is 845, with the total number of patients to be enrolled being 3,128 (1,564 in each arm).

Safety (non-inferiority): The primary safety endpoint is time to any hospitalisation or all-cause death. It is expected that the percentage of patients who have experienced this composite event by 5 years is 60%. Based on an assumed HR of 1, a non-inferiority margin of 1.2, a one-sided alpha of 0.025 and 90% power, the number of events required is 1,265, with the number of patients required being 2,108 (1,054 in each arm). Given the required sample size to demonstrate efficacy, it is therefore expected that the precision around the estimate for this endpoint will be higher.

Based on initial feasibility checks of semaglutide user numbers, we are unlikely to reach the number of patients and events as stated in the target trial protocol. To mitigate the risk of an underpowered study, we are collaborating with other research groups. An adapted protocol for these groups will be written. It is planned to meta-analyse results of these substudies.

8. Limitation of the methods

A grace period (90 days) is used to define the semaglutide treatment strategy for the primary analyses. This, along with the CCW approach, may induce similarity between the groups on endpoints that are expected to be observed relatively early into follow up (e.g. HF hospitalisation). Given some of the research questions addressed in this study are related to establishing non-inferiority, it is important to be mindful of this possibility. Sensitivity analyses with shorter grace periods will be performed.

As only covariate values at time 0 are to be used for weighting, there is a possibility that a time-varying confounder that is associated with treatment selection and the relevant outcome is omitted.

9. Protection of human subjects

No individual informed consent is necessary for data collection in the national registries and SwedeHF according to Swedish law. However, patients are informed of entry into SwedeHF and allowed to opt out.

10. Reporting of adverse events

The monitoring of adverse events is not relevant for this study. An objective of the study is to establish safety of semaglutide on clinical outcomes including all-cause hospitalisations and all-cause death. This is reflected in the definition of the primary and secondary endpoints.

11. Comparison between aspects of the target trial and emulation study

Target trial	**Observational study**	**Reason for difference (if relevant)**
Inclusion criteria		
Age ≥ 18 years	Age ≥ 18 years	
LVEF ≤ 40%	LVEF < 40%	Threshold in SwedeHF
NYHA class II-IV	NYHA class II-IV	
BMI ≥ 30 kg/m^2 (i.e. obese)	BMI ≥ 27 kg/m^2 (overweight or obese)	Due to feasibility concerns, the patient population was broadened to overweight or obese patients.
	Type 2 diabetes	Ozempic (semaglutide) is only indicated for patients with Type 2 diabetes. If Type 2 diabetes was not included as an eligibility criterion for the emulation study then the positivity assumption would have been violated. Type 2

		diabetes is also one of the comorbidities listed to allow for Wegovy use in overweight patients.
Exclusion criteria		
Diabetes mellitus other than type 2	Diabetes mellitus other than type 2	
Current or planned use of any GLP-1 RA	Current use of any GLP1-RA	Planned use cannot be identified
Use of any GLP-1 RA in the past 90 days	Use of any GLP1-RA in the past 180 days	Due to potential prescription hoarding the number of days without a GLP1-RA prescription was increased
Acute pancreatitis in prior 180 days	Acute pancreatitis in prior 180 days	
Any prior or ongoing diagnosis of chronic pancreatitis	Any prior or ongoing diagnosis of chronic pancreatitis	
Diagnosis of malignancies (exception: basal-cell carcinoma, squamous-cell carcinoma or carcinoma-in-situ, localised prostate cancer) in prior 5 years or still ongoing	Diagnosis of malignancies (exception: basal-cell carcinoma, squamous-cell carcinoma or carcinoma-in-situ, localised prostate cancer) in prior 5 years or still ongoing	
Allergy or severe intolerance against any component of treatment or placebo	-	This cannot be determined through registry data.
Pregnancy or breastfeeding during any time of the trial or women of child-bearing potential but without use of highly effective contraception during the trial and at least 2 months longer	-	Information is not available in the registry. Potential for pregnancy or breastfeeding, which leads to a patient not being eligible for receiving semaglutide will need to be acknowledged as a potential source of bias. Given the other inclusion criteria, the potential for pregnancy is likely to be low.
Any other condition that is likely to compromise the participant's safety or their compliance to the protocol in the investigator's opinion, incl. severe psychiatric disorders (only if lack of adherence to study protocol is expected)	-	As these are not formally contraindications for use of semaglutide, they are not considered to be relevant for the observational study.

The objectives and associated estimands are the same in the target trial and the emulation study. The current protocol for the emulation study does not address the exploratory endpoint of repeated (heart failure) hospitalisations. This is primarily due to the additional complexities of the statistical methods given the CCW approach. A separate statistical analysis plan will be written and a separate study performed to explore repeated events.

For heart-failure related hospitalisations, the broader definition of worsening heart failure has been narrowed to an event of heart failure hospitalisation.

As noted in the methods section, because the patients cannot be randomised at baseline to receive treatment or control the clone censor weight method is to be applied. This requires a grace period associated with a clinically plausible treatment strategy (i.e. receiving subcutaneous semaglutide within 90 days of eligibility) to be specified.

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13. Appendicies

Appendix A: Protocol for the hypothetical target trial: : https://catalogues.ema.europa.eu/node/4713/administrative-details

Appendix B: EMA-approved subcutaneous semaglutide indications (as of 30 January 2026) link: https://www.ema.europa.eu/en/medicines/human/EPAR/ozempic; https://www.ema.europa.eu/en/medicines/human/EPAR/wegovy