Semaglutide in patients with heart failure with reduced ejection fraction: safety and effectiveness – a target trial emulation

Part Ib: target trial protocol

Finalised protocol after external expert review

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Medical background

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 cardiovascular disease.[4,5]

Obese 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] A prespecified secondary analysis of the SELECT trial showed a consistent pattern of improved HF outcomes (composite of WHF and CV death) across HF phenotypes.[9] However, the benefit in HFrEF was primarily driven by CV death, with the point estimate for the HR for HF hospitalisations above 1 in patients with HFrEF.[9] In addition, doubts about the validity of the HFrEF diagnosis in SELECT (and others) have been raised based on unexpectedly low event rates in in the placebo arm.[10,11] In addition, some observational studies indicated potential benefits of semaglutide on HF outcomes across HF phenotypes.[12] Finally, the risk of potential harm by GLP-1 RA might be higher in patients in NYHA classes III/IV versus I/II or in those at elevated risk of malignant arrhythmia – suggesting some heterogeneity even within this HF phenotype.[11,13,14] 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.

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.[15] Consequently, the objectives of the present study are to 1) establish the efficacy of GLP-1 RA in 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.

Methods

Approach to the emulation of the target trial

This study will be conducted in three phases: First, a hypothetical target trial will be designed to address the research question. This target trial should be feasible in reality if sufficient funding and access to potential participants was available. A multi-disciplinary team of More-EUROPA researchers – represented by clinicians, registry experts, statisticians, regulators, and experts in clinical and observational study design – will define and reach consensus on the target trial design (Part Ia). This will be followed by a round of feedback provided by an independent expert in the field and respective revision of the target trial design (Part Ib). Part Ib will be uploaded to the HMA-EMA Catalogues of RWD studies before starting with Part II.[16] Expert feedback and response to the expert as well as a protocol version with track changes (Part Ia to Ib) are available from the authors upon request.

Second (Part II), the finalised target trial protocol will be operationalised for emulation with the data provided by the Swedish Heart Failure registry linked with other national registries, based on data availability, granularity as well as statistical and pathophysiological thinking. The reasoning of each step of the operationalisation will be made transparent.

Finally (Part III), the observational study will be performed accordingly, and the results will be published in a peer-reviewed journal.

Data sources

For the emulation of the target trial, data from five different Swedish quality registries will be used. The study population derives from the Swedish Heart Failure Registry (SwedeHF), managed by the Uppsala Clinical Research Center (Uppsala, Sweden), founded in 2000 and implemented nationwide in 2003.[17] Physician-judged HF is the only inclusion criterion, since April 2017 based on the International Statistical Classification of Diseases, 10th revision, Swedish version (ICD-10-SE) codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.6-7 or I50. Approximately 80 variables are recorded at the hospitalisation discharge or out-patient visit that prompts a registration. Until December 2023, 129,240 unique patients had been registered in SwedeHF, with 59% coverage of prevalent HF in Sweden in 2023.[18] The Swedish personal identification number allows for linkage between SwedeHF and other national registries.

Moreover, the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) managed by Statistics Sweden will provide socioeconomic variables.[19] The National Patient Register (NPR) contains data on diagnoses and procedures from in-patient stays since 1964 (nationwide 1987) and from specialist out-patient care (but not primary care) since 2001.[20] It will be used to supplement comorbidity variables in SwedeHF and to obtain cause-specific hospitalisation endpoints according to ICD-10-SE. The National Prescribed Drug Register (NPDR) was implemented in July 2005, and provides information based on the Anatomical Therapeutic Chemical classification (ATC) codes on prescribed drugs that were dispensed in pharmacies.[21] Information on cause-specific death will be collected through the National Cause of Death Register (CoD).[22] The NPR, NPDR, and CoD are all managed by the National Board of Health and Welfare.

Target trial protocol

Objectives

To establish the efficacy and safety of semaglutide (GLP-1 RA) in patients with HFrEF and obesity.

Eligibility criteria

Inclusion criteria

1. Age ≥ 18 years
2. LVEF ≤ 40%
3. NYHA class II-IV
4. BMI ≥ 30 kg/m^2
5. Written informed consent

Exclusion criteria

1. Diabetes mellitus other than type 2
2. Current or planned use of any GLP-1 RA
3. Use of any GLP-1 RA in the past 90 days
4. Acute pancreatitis in prior 180 days
5. Any prior or ongoing diagnosis of chronic pancreatitis
6. Diagnosis of malignancies (exception: basal-cell carcinoma, squamous-cell carcinoma or carcinoma-in-situ, localised prostate cancer) in prior 5 years or still ongoing
7. Allergy or severe intolerance against any component of treatment or placebo
8. Pregnancy or breastfeeding during anytime 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
9. 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)

Treatment strategies

Intervention arm: Standard of care for HF incl. 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.

Comparator arm: Standard of care for HF incl. dietary and lifestyle advice for weight reduction plus: completely inert placebo, subcutaneous injection.

Treatment assignment

1:1 randomisation, stratified by diabetes status

Start and end of follow-up

Start: at randomisation

End: death, end of trial, or after a maximum of 5 years

Research objectives, intercurrent events, and proposed strategies for efficacy and safety endpoints

Co-primary endpoint (efficacy)

- Time to first worsening HF event (WHF, i.e. HF hospitalisation or urgent out-patient visit due to HF*) or CV death (efficacy / superiority)

Co-primary endpoint (safety)

- Time to first all-cause hospitalisation or all-cause death (safety / non-inferiority)

Secondary endpoints: efficacy

- Time to CV death (efficacy / superiority)
- Time to first WHF event (efficacy / superiority)

Secondary endpoints: safety

- Time to all-cause death (safety / non-inferiority)
- Time to first all-cause hospitalisation (safety / non-inferiority)

Exploratory endpoints

- Total number of WHF events (efficacy / superiority)
- Total number of all-cause hospitalisations (safety / non-inferiority)

* Urgent out-patient visits due to HF are defined as unscheduled out-patient visits due to new or worsening signs or symptoms of HF with need for intravenous treatment with diuretics or inotropes.

Co-primary endpoint (efficacy)

Endpoint	Time to first WHF event or CV death (superiority)
Objective	To demonstrate that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is superior to SoC in terms of WHF events and CV death in patients with HFrEF and obesity.
Intercurrent event	**Strategy**
Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical
Change in HF therapy	Treatment policy
Non-CV death	Competing risk

Co-primary endpoint (safety)

Endpoint	Time to first all-cause hospitalisation or all-cause death (non-inferiority)
Objective	To establish that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is sufficiently safe in terms of all-cause hospitalisations and death compared with SoC in patients with HFrEF and obesity.
Intercurrent events	**Strategies**

Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical
Change in HF therapy	Treatment policy

Secondary endpoints: efficacy

Endpoint	Time to CV death (superiority)
Objective	To demonstrate that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is superior to SoC in terms of CV death in patients with HFrEF and obesity.
Intercurrent events	**Strategy**
Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical
Change in HF therapy	Treatment policy
Non-CV death	Competing risk

Endpoint	Time to first WHF event (superiority)

Objective	To demonstrate that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is superior in terms of WHF events compared with SoC in patients with HFrEF and obesity.
Intercurrent events	**Strategy**
Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical
Change in HF therapy	Treatment policy
All-cause death	Competing risk

Secondary endpoints: safety

Endpoint	Time to all-cause death (non-inferiority)
Objective	To establish that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is sufficiently safe in terms of mortality compared with SoC in patients with HFrEF and obesity.
Intercurrent events	**Strategies**
Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical

Change in HF therapy	Treatment policy

Endpoint	Time to first all-cause hospitalisation (non-inferiority)
Objective	To establish that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is sufficiently safe in terms of all-cause hospitalisations compared with SoC in patients with HFrEF and obesity.
Intercurrent events	**Strategy**
Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical
Change in HF therapy	Treatment policy
All-cause death	Competing risk

Exploratory endpoints

Endpoint	Total number of WHF events (superiority)
Hypothesis	To establish that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is superior in terms of WHF events compared with SoC in patients with HFrEF and obesity.

Intercurrent events	**Strategy**
Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical
Change in HF therapy	Treatment policy
Non-HF hospitalisation	Treatment policy (any HF-related events during hospital admission must be recorded)
All-cause death	Competing risk

Endpoint	Total number of all-cause hospitalisations (non-inferiority)
Objective	To establish that treatment with the GLP-1 RA semaglutide plus standard of care (SoC) is sufficiently safe in terms of the total number of all-cause hospitalisations compared with SoC in patients with HFrEF and obesity.
Intercurrent events	**Strategy**
Treatment discontinuation	Treatment policy
GLP-1 RA treatment switch/crossover	Hypothetical
Change in HF therapy	Treatment policy

All-cause death	Competing risk

Testing hierarchy

The endpoints will be tested in the following order. Both the efficacy co-primary endpoint (tested at one-sided alpha of 0.025) and the safety co-primary endpoint (based on the upper limit of the 95% CI of 1.2) need to be met in order for the secondary endpoints to be formally tested.

Following this, two hierarchies of secondary endpoints will be tested – one for efficacy and one for safety. If the test of an endpoint higher in the hierarchy is not significant (one-sided alpha of 0.025) or, for the safety endpoints, the boundary of the upper limit of the HR is crossed, then the endpoints further down that hierarchy will not be formally tested and will only be presented and interpreted descriptively.

For all safety endpoints, for which a non-inferiority margin has been specified, if non-inferiority/non-detriment can be concluded, then the same 95% confidence interval will also be used to evaluate superiority of GLP-1 RA compared with standard of care on the same endpoint.[23]

Overview of statistical methods planned for the target trial

Analysis datasets

The primary analysis will be on the full analysis dataset, including all participants who provided written informed consent and who were randomised. Participants will be analysed according to their allocated treatment group in line with the intention-to-treat principle.

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.

For the exploratory repeated event endpoints, the distribution of the number of events that occurred within each patient will be presented by arm, along with the mean cumulative function that takes the repeated events into account.[24]

Estimation and inference

A stratified Cox proportional hazards model will be used to estimate the HR (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.

Analyses will be stratified by diabetes mellitus (yes vs no). Secondary analyses will be performed with adjustment for the covariates as listed in the subgroup analyses section.

For the exploratory repeated event endpoints, the difference in the mean number of event months between the groups will be estimated by comparing the area under the mean cumulative function curves.[24] The fixed milestone time for this analysis will be 4 years.

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 GLP-1 RA 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 GLP-1 RA does not result in a (meaningful) negative effect.

Sample size estimation

Sample size calculations were performed using PASS version 24.0.2.

Efficacy (superiority): Based on available literature, it is expected that the proportion of patients in the comparator arm (SoC) who have experienced a WHF event or a CV-related death by 5 years after randomisation is 30%.[6,25] 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.

Censoring

ITT with no competing risks and hypothetical strategy for the intercurrent event of switching to another GLP-1 RA or crossover from placebo to semaglutide.

Patients will be followed up for the event of interest until the data-cut off/study end or until study withdrawal. Follow-up times will be censored for use of another GLP-1 RA or crossover from placebo to semaglutide. Patients who discontinue allocated treatment or have a change in HF background therapy without any treatment switching will continue to be followed up until the relevant timepoint.

ITT with the competing risk of (non-CV) death and a hypothetical strategy for the intercurrent event of switching to another GLP-1 RA or crossover from placebo to semaglutide.

Patients will be followed up for the event of interest until the data cut-off/study end or until study withdrawal. Follow-up times will be censored at use of another GLP-1 RA or crossover from placebo to semaglutide. Patients who discontinue allocated treatment or have a change in HF background therapy without any treatment switching will continue to be followed up until the relevant timepoint. For patients who have a competing risk of (non-CV) death, the patient will be removed from the at-risk set at the time of the relevant competing event.

Supplemental estimands and sensitivity analyses

For all safety endpoints, a supplemental analysis will be performed for which the patients are analysed 'as treated', i.e. based on the treatment received regardless of randomised group.

For any GLP-1 RA treatment switches or crossover from placebo to GLP-1 RA, two sensitivity/supplemental analyses are planned: (1) a sensitivity analysis will be performed for which any relevant events within a time window of 30 days after switch will be counted to take into account any delayed impact of the allocated treatment; (2) a supplemental estimand will be targeted for which a treatment policy strategy is used to address treatment switching (i.e. the event is counted regardless of switching to another GLP-1 RA or from comparator to treatment arm).

For patients who crossover from the comparator arm to receive GLP-1 RA, descriptive statistics of their safety outcomes will be provided.

Subgroup analyses

Prespecified subgroup analyses will be performed based on physiological reasoning and prior evidence:

- Age (< 50, 50-69, ≥ 70 years)
- SGLT2i (yes vs no)
- Diabetes mellitus (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/m^2 vs ≥ 35 kg/m^2)
- eGFR (< 30, 30-60, > 60 ml/min/1.73m^2)

Supplement: reasoning for target trial design

Design & aim

The target trial is designed to assess efficacy and safety of GLP-1 RA in patients with HFrEF based on previously published safety concerns and as outlined in the Background section. In line with this aim, the trial is designed to address the question of whether we can be sufficiently reassured that there are no negative effects of GLP-1 RA on important safety endpoints, particularly all-cause death and all-cause hospitalisations, in addition to efficacy.

Inclusion criteria

In the present target trial, no enrichment strategies to select a population at elevated risk of adverse events (e.g. prior HF hospitalisation or NT-proBNP cut-offs) need to be applied. These strategies aim at reducing the necessary number of participants to achieve sufficient power, hereby reducing cost and recruitment time. In the present target trial, which is designed for ideal circumstances, no such limitations apply.

For both legal and ethical reasons, only participants of at least 18 years of age are included. In addition, they must provide written informed consent.

We decided to require a BMI of at least 30 kg/m^2 as this is the expected group of patients with HFrEF that would be most likely to receive GLP-1 RA without any further comorbidities. Although Wegovy has an approved indication for patients with a BMI between 27 kg/m^2 and 30 kg/m^2 with additional weight-related conditions, we have thus decided to first focus on the patent group with at least 30 kg/m^2. Patients with a BMI below should be the focus of further research.

While safety concerns for GLP-1 RA use exist primarily in patients with HFrEF, little is known about patients with HFmrEF, as parts of this entity are usually counted towards either HFpEF or HFrEF in RCTs: in the landmark trials STEP-HFpEF and the STEP-HFpEF DM, only patients with $\geq$ 45% LVEF (i.e. including the upper part of the HFmrEF spectrum) were included.[26,27] In the SUMMIT trial, only patients with HFpEF as defined by the guidelines (i.e. $\geq$ 50% LVEF) were included.[28] 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 $\leq$ 40%. In this population, we consider there to be the greatest scientific equipoise, primarily due to the lack of robust data, which provides a strong rationale for the present target trial.

NYHA class of II or greater is necessary to increase validity of the HF diagnosis (i.e. excluding asymptomatic left ventricular dysfunction; not considered as an enrichment strategy).

Exclusion criteria

The exclusion criteria are largely in line with other RCTs 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). Unlike some trials, we decided not to add severe renal or hepatic dysfunction as exclusion criteria; by authorised label, these conditions are no contraindications, albeit particular caution is advised.

Treatment strategies, assignment, and implementation

The treatment strategy for GLP-1 RA is in line with the prescribing guidelines. The SoC of usual HF treatment and dietary and lifestyle advice is in line with the care that would be provided to patients with a BMI ≥ 30 kg/m^2 by a treating physician in the absence of GLP-1 RA.

Endpoints

The specification of co-primary endpoints reflects the objective to establish both overall efficacy in the study population and to more formally establish that the treatment is safe. The approach to specifying an upper bound of the confidence interval this is in line with EMA guidance.[29]

The secondary and exploratory endpoints investigate specific efficacy and safety endpoints further.

Follow-up

It is considered that the follow-up time of 5 years is sufficient to evaluate the primary efficacy endpoint as well as to provide reassurance on safety in terms of all-cause hospitalisations and all-cause mortality.

Causal estimand

The estimands including the intercurrent events and strategies as described for each endpoint address the relevant research questions.

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