

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

First published: 10/11/2025

Last updated: 10/11/2025

Study

Planned

Administrative details

EU PAS number

EUPAS1000000809

Study ID

1000000809

DARWIN EU® study

No

Study countries

- France
 - Netherlands
 - Portugal
 - Sweden
-

Study description

Efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as semaglutide in patients with heart failure with reduced ejection fraction (HFrEF) remain unclear. Existing evidence is limited to post-hoc analyses or observational studies, often with uncertain validity of the HFrEF diagnosis. While the ongoing FIT-HF trial in HFrEF focuses on peak oxygen uptake as the primary outcome, no trial is currently addressing efficacy and safety. We aim to fill this gap by conducting a high-quality target trial emulation using the Swedish national quality and administrative registries.

Study status

Planned

Research institutions and networks

Institutions

[Radboud university medical center \(Radboudumc\)](#)

Netherlands

First published: 30/06/2022

Last updated: 21/03/2025

Institution

Educational Institution

Hospital/Clinic/Other health care facility

ENCePP partner

[Karolinska Institutet](#)

Sweden

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Educational Institution

Centre for Research Epidemiology and Statistics
(Paris, France)

Networks

More-EUROPA (Horizon Europe)

Contact details

Study institution contact

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Primary lead investigator

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 07/04/2025

Actual: 07/04/2025

Study start date

Planned: 15/12/2025

Data analysis start date

Planned: 02/01/2026

Date of final study report

Planned: 30/06/2026

Sources of funding

- EU institutional research programme

More details on funding

More Effectively Using Registries to support Patient-centered Regulatory and HTA decision-making (More-EUROPA), Grant agreement ID: 101095479, Horizon Europe programme

Study protocol

[2025-11-04a GLP-1 RA target trial protocol_Part Ib.pdf](#) (351.97 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Method development or testing

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

- 1) Design of a target trial (i.e. a randomised controlled trial protocol)
- 2) Emulation of the target trial with real-world data

Main study objective:

To evaluate effectiveness and safety of semaglutide in patients with heart failure with reduced ejection fraction (HFrEF) and obesity.

Study Design

Non-interventional study design

Cohort

Other

Non-interventional study design, other

target trial emulation

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

SEMAGLUTIDE

Anatomical Therapeutic Chemical (ATC) code

(A10BJ06) semaglutide

semaglutide

Medical condition to be studied

Heart failure with reduced ejection fraction

Obesity

Population studied

Short description of the study population

Adult patients with heart failure with reduced ejection fraction (HFrEF) and obesity in New York Heart Association (NYHA) classes II-IV.

Age groups

- **Adult and elderly population (≥ 18 years)**

- Adults (18 to < 65 years)
 - Adults (18 to < 46 years)
 - Adults (46 to < 65 years)
 - Elderly (≥ 65 years)
 - Adults (65 to < 75 years)
 - Adults (75 to < 85 years)
 - Adults (85 years and over)
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Special population of interest

Frail population

Hepatic impaired

Renal impaired

Study design details

Setting

TARGET TRIAL

The hypothetical target trial would most likely be conducted as a multi-centre, international trial. For further details, please refer to the uploaded target trial protocol (file: 2025-11-04a GLP-1 RA target trial protocol_Part Ib).

EMULATED TRIAL

Patients registered to the Swedish Heart Failure Registry (SwedeHF) by participating healthcare centres in Sweden. Further details will be provided as soon as the observational study protocol is finalised.

Comparators

TARGET TRIAL

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

EMULATED TRIAL

Further details will be provided as soon as the observational study protocol is finalised.

Outcomes

TARGET TRIAL

Co-primary endpoint (efficacy)

- Time to first worsening heart failure event (i.e. heart failure hospitalisation or urgent out-patient visit due to heart failure) or cardiovascular death (efficacy / superiority)

Co-primary endpoint (safety)

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

For secondary and exploratory outcomes, please refer to the uploaded target trial protocol (file: 2025-11-04a GLP-1 RA target trial protocol_Part Ib).

EMULATED TRIAL

Further details will be provided as soon as the observational study protocol is

finalised.

Data analysis plan

TARGET TRIAL

Please refer to the uploaded target trial protocol (file: 2025-11-04a GLP-1 RA target trial protocol_Part Ib).

EMULATED TRIAL

Further details will be provided as soon as the observational study protocol is finalised.

Summary results

The study group reached a consensus on the target trial protocol on November 1, 2025, after review by an external expert. The protocol was uploaded to the HMA-EMA Catalogues (file: 2025-11-04a GLP-1 RA target trial protocol_Part Ib). The study group started working on the emulation into the observational study on November 10, 2025, after the target trial protocol had been finalised.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Swedish Cause of Death Register

Sweden National Prescribed Drugs Register / Läkemedelsregistret

Data source(s), other

Swedish Heart Failure Registry (SwedeHF)

Swedish National Patient Register (NPR)

Swedish Longitudinal Integrated Database for Health Insurance and Labour (LISA)

Swedish Total Population Register

Data sources (types)

[Administrative healthcare records \(e.g., claims\)](#)

[Death registry](#)

[Disease registry](#)

[Drug prescriptions](#)

[Population registry](#)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Not applicable