TARGET EU: The risk of angiooedema and other safety events in heart failure patients treated with sacubitril/valsartan compared to angiotensin-converting enzyme inhibitors

First published: 26/05/2026

Last updated: 26/05/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS1000001002

Study ID

1000001002

DARWIN EU® study

No

Study countries

Netherlands

United Kingdom

Study description

This case study is part of the broader TARGET EU project (EUPAS1000000539), which aims to advance the regulatory use of real-world data through the application of target trial emulation and estimand methodologies.

Background: Sacubitril/valsartan (SV) was superior to enalapril, an Angiotensin Converting Enzyme Inhibitor (ACEI), in delaying the time to the composite outcome of Heart Failure (HF) hospitalization or cardiovascular death in patients with Heart Failure and reduced Ejection Fraction (HFrEF) in the PARADIGM-HF trial. Angioedema was a safety outcome of special interest with a relative risk of 1.9 (95% CI 0.8-4.5) for the SV arm vs the enalapril arm. Nevertheless, the PARADIGM-HF population may not be fully representative of the real-world HF population and angioedema is a rare event, both of which render necessary the assessment of the risk of angioedema with SV on a larger scale and in the general HF population.

Objectives: The primary objective is to estimate the effect of treatment with SV vs ACEi on time to first angioedema event in patients with HF.

Methods: We will perform a Prevalent New User active comparator cohort study using linked electronic healthcare records from the UK CPRD Aurum and the Netherlands PHARMO. Eligible patients are adults with HF, initiating SV or treated with ACEI from 01/01/2014 until 31/03/2023 and September 2024 for CPRD and PHARMO, respectively. In the primary analysis a while on treatment strategy is used for treatment - related intercurrent events and a while alive strategy for all-cause mortality. We match new SV users with ACEI users based on their treatment history before the index date and on time-conditional propensity score. In the primary analysis we use a Cox proportional hazards model with supplemental analyses using an accelerated model to estimate restricted mean survival time at 3 and 5 years. Sensitivity analyses will assess

the impact of departures from key assumptions.

Study status

Ongoing

Research institutions and networks

Institutions

Electronic Health Records (EHR) Research Group, London School of Hygiene & Tropical Medicine (LSHTM)

United Kingdom

First published: 19/04/2010

Last updated: 30/10/2024

Institution | Educational Institution | ENCePP partner

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 27/05/2026

Institution | Educational Institution | ENCePP partner

Clinical Practice Research Datalink (CPRD)

United Kingdom

First published: 15/03/2010

Last updated: 17/01/2025

Institution | Laboratory/Research/Testing facility | ENCePP partner

Clinical Pharmacology, Vall d'Hebron Institut de Recerca (VHIR)

Spain

First published: 18/05/2021

Last updated: 20/05/2021

Institution | Outdated | Hospital/Clinic/Other health care facility | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

Netherlands

First published: 07/01/2022

Last updated: 19/12/2025

Institution | Non-Pharmaceutical company | ENCePP partner

Teamit Institute

Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

Belgium

Denmark

Finland

France

Germany

Italy

Netherlands

Norway

Spain

United Kingdom

First published: 22/09/2020

Last updated: 22/09/2020

Network | Outdated | ENCePP partner

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

Netherlands

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Network

Contact details

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Study timelines

Date when funding contract was signed
Planned: 19/09/2024

Actual: 19/09/2024

Study start date
Planned: 09/03/2026

Actual: 09/03/2026

Data analysis start date
Planned: 09/03/2026

Date of final study report
Planned: 10/06/2026

Sources of funding

- EMA

Study protocol

Emulation_Protocol_CS6_REV5_clean.pdf (1.18 MB)

CS6_Feasibility Assessment.pdf (416.98 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:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

To emulate the target trial, we will use the prevalent new user (PNU) cohort design. This design includes an active comparator per definition. It matches

new users of SV to ACEI comparators on their prior treatment history with ACEI/ARB.

Main study objective:
The primary objective of this observational study is to estimate the effect of treatment with sacubitril/valsartan versus ACEi on time to first angioedema event in patients with HF while the patients remain alive and while on treatment, i.e. before treatment discontinuation, switching or new add-on of any of the three HF medications (ACEi, ARB, SV).

Study Design

Non-interventional study design
Cohort

Study drug and medical condition

Medicinal product name
ENTRESTO

Anatomical Therapeutic Chemical (ATC) code
(C09DX04) valsartan and sacubitril
valsartan and sacubitril

Medical condition to be studied
Heart failure with reduced ejection fraction
Heart failure with midrange ejection fraction
Heart failure with preserved ejection fraction

Population studied

Short description of the study population

This study will be conducted using routinely collected electronic health records from 2014 to 2023 and to 2024, for the CPRD and PHARMO databases, respectively. It will be set primarily in primary care and will draw on longitudinal data from general practices, with linkage to hospital and mortality records. Data will be sourced from two European countries: the United Kingdom and the Netherlands. In the UK, data will be obtained from the Clinical Practice Research Datalink (CPRD) Aurum database while in the Netherlands, data will be obtained from the PHARMO database.

The study population will consist of adults with HF who initiate SV or are treated with ACEIs during the study period. Cohort entry (index date) will be defined as the date of the first SV prescription or the matched ACEI prescription (matched ACEI prescription is identified after applying the prevalent new user design). To be eligible, individuals must have a recorded diagnosis of HF prior to the index date and be aged 18 years or older at cohort entry. In addition, individuals must have at least one year of recorded medical history prior to the index date to allow adequate assessment of baseline characteristics. Several exclusion criteria will be applied to ensure appropriate cohort definition. Individuals will be excluded if they have a history of angioedema or severe hepatic impairment at any time before index date. They will also be excluded if they have overlapping prescriptions for ACEIs and ARBs in the 60 days before index date, a hospitalization for HF in the 7 days before index date, a diagnosis of peripartum cardiomyopathy or cardiomyopathy induced by external agents in the 1 year before index date and a diagnosis of hyperkalaemia or hypotension in the 30 days before index date.

Overall, the final study population will comprise adults aged 18 years or older with HF diagnosis who newly initiate SV or are treated with ACEI between 2014

and 2023 or 2024, for CPRD and PHARMO, respectively and meet all inclusion and exclusion criteria.

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)

Study design details

Setting

This study is conducted using routinely collected electronic health records from 2014 to 2024, reflecting the period of SV use in routine clinical practice. The study is set primarily in primary care, drawing on longitudinal data from general practices with linkage to hospital data. Data are sourced from two European countries, the United Kingdom (Clinical Practice Research Datalink [CPRD]) and Netherlands (PHARMO), providing population-based and representative coverage of real-world clinical care.

Comparators

We chose an active comparator design because it is the most appropriate for the observational study, considering also that HF patients are likely already being treated. The 2021 guidelines of European Society of Cardiology recommend ACEIs or SV among the treatments of the first-line therapy of HF

with reduced or mildly reduced ejection fraction. SV is also recommended as a replacement of ACEIs in suitable patients who remain symptomatic despite optimal treatment with all the recommended first line treatments. ARBs are considered as an alternative option in patients who are intolerant to ACEIs. Considering this information, ACEIs are the most appropriate comparator in our study.

Outcomes

Angioedema is a safety outcome of particular interest because of the mechanism of action of both the intervention treatment and the control. From a clinical perspective it is important to know the risk of angioedema that treatments are associated with for two reasons. First and foremost, because it may necessitate hospitalization and may be life-threatening when it involves the upper airway. Secondly, because it usually leads to treatment discontinuation, which is the only way it can be addressed, depriving patients of the beneficial effects of HF treatments.

Data analysis plan

The analyses are conducted within a target trial emulation framework to estimate the effect of SV compared with ACEIs on the risk of angioedema.

For Estimand 1, the main estimand supporting decision making, the primary causal effect summary measure is the hazard ratio for time to first angioedema using a stratified Cox proportional hazards model in the PSM sample. The Cox model will be fitted separately within each data source (CPRD and BIFAP), and the resulting hazard ratios will be combined using a random-effects meta-analysis; potential sources of heterogeneity will be described qualitatively, including structural differences (e.g., coding systems, population coverage) and measurement differences (e.g., recording practices) and their implications (e.g.,

residual confounding or misclassification).

Sensitivity analyses will assess robustness of the primary findings to key assumptions, including inverse probability of censoring weighting (IPCW), best/worst case scenario, and probabilistic bias analysis for non-differential outcome misclassification (details in Section 7.6.5).

Two supplemental estimands are also defined: Estimand 2, applying a treatment policy strategy for intercurrent events, and Estimand 3, estimating treatment effects using restricted mean survival time (RMST) derived from a PSM Weibull accelerated failure time (AFT) model. In addition, supplemental analyses (e.g., crude and PS-matching adjusted Kaplan–Meier curves, crude Cox models, event counts and incidence rates, propensity score and weight distributions, covariate balance before and after PSM, censoring and intercurrent event patterns, proportional hazards diagnostics, positivity checks, and multiple-imputation diagnostics) will be conducted to support interpretation of the main analysis.

Summary results

Not yet available

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)

Clinical Practice Research Datalink

PHARMO Data Network

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

ConcepTION CDM

CDM website

https://www.imi-conception.eu/

CDM release frequency

6 months

CDM version

V 2.2

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation details

The feasibility assessment for this case study, detailed in the appendix of the study protocol, was conducted as part of the broader TARGET-EU feasibility assessment (EUPAS1000000791). Data source suitability was evaluated using a structured framework based on the EMA data quality framework, assessing system characteristics, data quality, and fitness for the research question. Briefly, both CPRD and PHARMO were deemed feasible data sources for studying SV and the risk of angioedema, with achievable sample sizes and reasonably up-to-date data. Both data sources provide data of good recency but certain limitations were identified. For CPRD these were that it lacks dispensing information and may have incomplete diagnostic coding in some settings, while for PHARMO this was that it has 70%-100% completeness in most of the

variables.

Data characterisation details

CS6_Feasibility Assessment.pdf

English (416.98 KB - PDF)

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