DARWIN EU® - Incidence of myoclonus in heart failure: a descriptive analysis in patients treated with sacubitril/valsartan and other treatments

First published: 30/10/2024

Last updated: 10/08/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000351

Study ID

1000000351

DARWIN EU® study

Yes

Study countries

Germany

Spain

United Kingdom

Study description

Sacubitril/valsartan (Entresto) is an angiotensin receptor-neprilysin inhibitor used to treat symptomatic chronic heart failure in both adults and children. Its dual mechanism of action involves inhibiting neprilysin and blocking the angiotensin II type-1 receptor, providing complementary cardiovascular benefits. The Pharmacovigilance Risk Assessment Committee (PRAC) is currently investigating a signal on a potential association between the use of sacubitril/valsartan and myoclonus.

Through this study, we aimed to investigate the incidence rate of myoclonus in the general population, newly diagnosed heart failure patients and patients with heart failure initiating sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs).

This study aims to estimate incidence rates of myoclonus in different populations of interest.

Specific study objectives:

1. To calculate the incidence rate of myoclonus in a newly diagnosed heart failure population and the general population, stratified by age groups and sex.
2. To calculate the incidence rate of myoclonus in a heart failure population following first initiation of treatment cohorts: sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) (index date being the start of the treatment).

Study status

Ongoing

Research institutions and networks

Institutions

Department of Medical Informatics - Health Data Science, Erasmus Medical Center (ErasmusMC)

Netherlands

First published: 03/11/2022

Last updated: 02/05/2024

Institution | Educational Institution | ENCePP partner

Networks

Data Analysis and Real World Interrogation Network (DARWIN EU®)

- Belgium
- Croatia
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Italy
- Netherlands
- Norway
- Portugal

Spain

Sweden

United Kingdom

First published: 01/02/2024

Last updated: 30/04/2025

Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Julieta Politi

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 23/09/2024

Actual: 23/09/2024

Study start date

Planned: 22/10/2024

Actual: 22/10/2024

Date of final study report
Planned: 06/01/2025

Sources of funding

- EMA

Study protocol

DARWIN EU_Protocol_P3-C1-015_Sacubitril valsartan and risk of myoclonus V4.pdf (831.26 KB)

Regulatory

Was the study required by a regulatory body?

Yes

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

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:

The incidence of the event of interest will be assessed using a population-level descriptive epidemiology design.

Main study objective:

1. To calculate the incidence rate of myoclonus in a newly diagnosed heart failure population and the general population, stratified by age groups and sex.
2. To calculate the incidence rate of myoclonus in a heart failure population following first initiation of treatment cohorts: sacubitril/valsartan, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) (index date being the start of the treatment).

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

ENTRESTO

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

SACUBITRIL

VALSARTAN

Anatomical Therapeutic Chemical (ATC) code

(C09DX04) valsartan and sacubitril

valsartan and sacubitril

Medical condition to be studied

Myoclonus

Population studied

Short description of the study population

The source population will include all patients present in the database from January 1st, 2015 (first EU approval of sacubitril/valsartan) to 31st December 2023 (or the last available date). All patients will be required to have at least 365 days of observation time before the index date and be 18 years of age or above at index date.

Study design details

Setting

This study used routinely collected health data from 3 databases in the DARWIN EU® network of data partners from 3 European countries.

Outcomes

Incident myoclonus in line with the PRAC signal

Summary results

In this disease epidemiology study of myoclonus in patients with incident HF, HF newly initiating treatments of interest (ACEi, ARBs, and sacubitril/valsartan first and later lines), and the general population in UK, Germany, and Spain, we found that patients with incident HF consistently exhibited higher incidence rates of myoclonus broad and narrow outcomes, when compared to both the HF newly-initiating treatments of interest and general populations. For myoclonus broad, the highest rates for the incident HF and treatment initiator cohorts occurred within the 0-30 days following the start of follow-up. Among new initiators of different treatments of interest in the HF population, when estimable, rates for myoclonus broad were highest among ARBs initiators, and results do not support higher rates among sacubitril/valsartan (later line) treatment. While no significant increase in myoclonus rates was observed across treatment groups, findings should be interpreted with caution due to low event counts, especially for sacubitril/valsartan first line initiators, where numbers were generally too low to provide precise estimates.

Documents

Study report

DARWIN EU_Report_P3-C1-015_Sacubitril valsartan and risk of myoclonus V3.pdf (2.33 MB)

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)

The Information System for Research in Primary Care (SIDIAP)

IQVIA Disease Analyzer Germany

Clinical Practice Research Datalink (CPRD) GOLD

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

https://ohdsi.github.io/CommonDataModel/index.html

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown