# Non-interventional post-authorization multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of sacubitril/valsartan (Entresto®)

**First published:** 31/03/2017

**Last updated:** 11/07/2025

Study | Finalised

## Administrative details

**EU PAS number**

EUPAS18358

**Study ID**

49003

**DARWIN EU® study**

No

**Study countries**

- [ ] Denmark
- [ ] Germany
- [ ] Italy
- [ ] Netherlands
- [ ] Spain
- [ ] United Kingdom

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**Study description**

Sacubitril/valsartan is a novel treatment initially approved in the United States, and the EU in 2015. It is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Based on the observation that sacubitril inhibits OATP1B1 and OATP1B3 transporters in vitro, a drug-drug interaction (DDI) study with atorvastatin (a HMG-CoA reductase inhibitor statin and OATP1B1 and OATP1B3 substrate) showed that sacubitril/valsartan increased the maximal plasma concentrations of atorvastatin and its metabolites by up to 2-fold.

However, the areas under the curve of atorvastatin and its metabolites were not increased to a clinically significant extent.

Based on the above, and given the high proportion of patients expected to be on a concomitant statin post-marketing, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis to further evaluate this potential DDI in the post-marketing setting.

Novartis therefore committed to perform a case-control study to assess specific statin-associated safety events (namely myotoxicity, hepatotoxicity, and acute pancreatitis) in statin-exposed heart failure (HF) patients with or without concomitant use of sacubitril/valsartan using information from five European healthcare databases (i.e. CPRD Clinical Practice Research Datalink from the UK, PHARMO The PHARMO Database Network from the Netherlands, SIDIAP Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) from Catalonia, Spain, HSD Health Search IMS Health Longitudinal

Patient Database from Italy, and the Aarhus University Prescription Database and Danish National Patient Registry from Denmark).

**Study status**

Finalised

# Research institutions and networks

## Institutions

### Novartis Pharmaceuticals

**First published:** 01/02/2024

**Last updated:** 01/02/2024

Institution

### Leibniz Institute for Prevention Research and Epidemiology - BIPS

Germany

**First published:** 29/03/2010

**Last updated:** 30/03/2026

Institution | Not-for-profit | 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

## Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

**First published:** 05/10/2012

**Last updated:** 23/05/2025

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

## Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford

United Kingdom

**First published:** 01/02/2024

**Last updated:** 01/02/2024

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

## Aarhus University Hospital

**First published:** 01/02/2024

**Last updated:** 01/02/2024

Institution

## Società Italiana di Medicina Generale e delle Cure Primarie (SIMG)

**First published:** 01/02/2024

**Last updated:** 01/02/2024

Institution | Patient organisation/association

## Agenzia regionale di sanità della Toscana (ARS Toscana)

Italy

**First published:** 01/02/2024

**Last updated:** 23/03/2026

Institution | EU Institution/Body/Agency | ENCePP partner

## Basel Pharmacoepidemiology Unit, University of Basel

**First published:** 01/02/2024

**Last updated:** 01/02/2024

Institution

## Contact details

**Study institution contact**

Novartis Clinical Disclosure Office

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Study contact

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**Primary lead investigator**

Novartis Clinical Disclosure Office

Primary lead investigator

## Study timelines

**Date when funding contract was signed**

Planned: 01/04/2017

Actual: 02/06/2017

**Study start date**

Planned: 30/06/2017

Actual: 01/09/2017

**Date of interim report, if expected**
Planned: 31/12/2017

Actual: 15/03/2018

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**Date of final study report**
Planned: 25/11/2024

Actual: 03/10/2024

## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

Novartis Pharma AG

## Study protocol

LCZ696B2015-Redacted-Protocol.pdf (1.44 MB)

LCZ696B2015-v02-Redacted-Protocol.pdf (529.62 KB)

## Regulatory

**Was the study required by a regulatory body?**

Yes

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

EU RMP category 3 (required)

# Other study registration identification numbers and links

CLCZ696B2015

# Methodological aspects

## Study type

## Study type list

**Study type:**

Non-interventional study

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**Scope of the study:**

Safety study (incl. comparative)

**Data collection methods:**

Secondary use of data

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**Main study objective:**

To assess individually the relative risk of myotoxic events, hepatotoxic events, and acute pancreatitis associated with concomitant exposure of LCZ696 together with statins compared with statin exposure alone in adult patients with HF using real-world data.

## Study Design

**Non-interventional study design**

Case-control

## Study drug and medical condition

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

SACUBITRIL

VALSARTAN

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**Anatomical Therapeutic Chemical (ATC) code**

(C09DX04) valsartan and sacubitril

valsartan and sacubitril

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**Medical condition to be studied**

Chronic left ventricular failure

## Population studied

**Short description of the study population**

Adult patients with heart failure

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**Age groups**

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

## Study design details

**Outcomes**

Myotoxic events

Hepatotoxic events

Acute pancreatitis

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**Data analysis plan**

Demographic and clinical characteristics of case and control patients at the index date were described separately for each outcome of interest using contingency tables for categorical variables and mean, standard deviation (sd), range, median and interquartile range (IQR) for continuous variables in each individual database.

Conditional logistic regression analyses were used to estimate crude and adjusted odds ratios (ORs) of each specific outcome with corresponding 95% confidence intervals (CIs).

The primary analysis was current LCZ696 and statin versus current use of statin (any dose) without current use of LCZ696. Secondary analyses comprised investigation of dose of statin and duration of LZC696, recent use of LZC696 or statins, and individual statins.

In dose specific analysis for statins the reference category was current low dose of statins and non-use of LCZ696. Control for confounding was based on matching (1:4 case: control ratio) and confounder adjustment.

# Documents

**Study report**

LCZ696B2015_Final-Study-Report_for redaction_Redacted.pdf (4.29 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)**

Clinical Practice Research Datalink

Danish registries (access/analysis)

Health Search/IQVIA Health Longitudinal Patient Database

The Information System for Research in Primary Care (SIDIAP)

PHARMO Data Network

German Pharmacoepidemiological Research Database

ARS Toscana

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**Data sources (types)**

Administrative healthcare records (e.g., claims)

Drug prescriptions

Electronic healthcare records (EHR)

Pharmacy dispensing records

# Use of a Common Data Model (CDM)

**CDM mapping**

Yes

**CDM Mappings**

**CDM name (other)**

# Data quality specifications

**Check conformance**

Unknown

**Check completeness**

Unknown

**Check stability**

Unknown

**Check logical consistency**

Unknown

# Data characterisation

**Data characterisation conducted**

Unknown