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

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: 09/07/2026

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

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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

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

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

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

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

Anatomical Therapeutic Chemical (ATC) code

(C09DX04) valsartan and sacubitril

valsartan and sacubitril

Medical condition to be studied

Chronic left ventricular failure

Population studied

Short description of the study population

Adult patients with heart failure

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

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

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