Non-interventional post-authorization multidatabase 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: 11/02/2025



Administrative details

PURI

https://redirect.ema.europa.eu/resource/49003

EU PAS number

EUPAS18358

Study ID

49003

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

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Leibniz Institute for Prevention Research and Epidemiology - BIPS

Germany

First published: 29/03/2010

Last updated: 26/02/2024



The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

Netherlands

First published: 07/01/2022

Institution	Laboratory/Research/Testing facility	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: 23/02/2024



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

United Kingdom

First published: 01/02/2024



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



Patient organisation/association

Agenzia regionale di sanità della Toscana (ARS)

Italy

First published: 01/02/2024

Last updated: 12/03/2024



EU Institution/Body/Agency

ENCePP partner

Basel Pharmacoepidemiology Unit, University of Basel

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Contact details

Study institution contact Novartis Clinical Disclosure Office

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 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

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

Data analysis plan

Demographic and clinical characteristics of case and control patients at the index date will be 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 will be used to estimate crude and adjusted odds ratios (ORs) of each specific outcome with corresponding 95% confidence intervals (CIs). The primary analysis is current LCZ696 and statin versus current use of statin (any dose) without current use of LCZ696. Secondary analyses comprise 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 will be current low dose of statins and non-use of LCZ696. Control for confounding will be based on matching (1:4 case: control ratio) and confounder adjustment.

Data management

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 dispensing/prescription data

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name (other)

Study specific CDM

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown