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: 02/04/2024

Study | Ongoing

Administrative details

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

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
Ongoing

Research institution and networks

Institutions

Novartis Pharmaceuticals
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Institution

Basel Pharmacoepidemiology Unit Switzerland

Contact details

Study institution contact

Novartis Clinical Disclosure Office
Study contact

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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:
31/12/2022

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:
Assessment of risk minimisation measure implementation or effectiveness

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 rea-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
100000166629
valsartan and sacubitril

Medical condition to be studied
Chronic left ventricular failure

Population studied

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)

Estimated number of subjects
7117

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 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 data (e.g. claims)
Drug dispensing/prescription data
Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping
No

Data quality specifications

Check conformance
Unknown

Check completeness
Unknown

Check stability
Unknown

Check logical consistency
Unknown

Data characterisation

Data characterisation conducted
No