Non-interventional post-authorization multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with use of Entresto® (sacubitril/valsartan) in adult patients with heart failure

First published: 24/03/2017

Last updated: 11/02/2025

Study Finalised

Administrative details

PURI

https://redirect.ema.europa.eu/resource/49019

EU PAS number

EUPAS18214

Study ID

49019

DARWIN EU® study

No

Study countries

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

Study description

Sacubitril/valsartan exhibits a novel mechanism of action to treat heart failure (HF) by simultaneously inhibiting neprilysin (neutral endopeptidase, NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. It was approved in the European Union (EU) in November 2015 for treatment of symptomatic chronic heart failure with reduced ejection fraction. As agreed with the Committee for Medicinal Products for Human Use (CHMP), the Marketing Authorisation Holder of Sacubitril/valsartan will conduct a non-imposed non-interventional Post-Authorization Safety Study (PASS, category 3) to estimate the incidence and relative risks of angioedema, as well as the incidence of hypotension, hyperkalaemia, hepatotoxicity, and renal impairment in adult patients diagnosed with HF (prevalent and incident) newly starting sacubitril/valsartan or using angiotensin-converting enzyme inhibitors (ACEIs). Therefore, a multi-database cohort study with secondary use of five European healthcare databases will be performed. The following databases will be used: CPRD (The 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: 26/02/2024

Institution | Not-for-profit | ENCePP partner

The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

Netherlands

First published: 07/01/2022

Last updated: 24/07/2024

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

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)

Italy

First published: 01/02/2024

Last updated: 12/03/2024

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 Officer

Study contact

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Primary lead investigator

Novartis Clinical Disclosure Officer

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 01/04/2017

Actual: 08/06/2017

Study start date

Planned: 30/06/2017

Actual: 01/09/2017

Date of interim report, if expected
Planned: 31/03/2018

Actual: 14/03/2018

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

Actual: 09/10/2024

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Novartis Pharma AG

Study protocol

LCZ696B2014-Redacted-Protocol.pdf(1.23 MB)

LCZ696B2014-v01.1--protocol_15Sep2022_Redacted.pdf(1.58 MB)

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

Study design:

A non-interventional, cohort study using European healthcare database information in a population of adult patients with prevalent or incident HF, newly starting treatment with sacubitril/valsartan (with or without prior exposure to ACEIs or ARBs), or ACEIs (as new users, and prevalent users).

Main study objective:

The primary objectives of the study were:

- To estimate the incidence of specific safety events of interest in adult patients with HF newly starting treatment with sacubitril/valsartan (regardless of prior exposure to ACEIs or angiotensin receptor blockers [ARBs]).
- To estimate the incidence of all safety events of interest in adult HF patients

newly starting treatment with sacubitril/valsartan without prior exposure to ACEIs or ARBs.

Study Design

Non-interventional study design

Cohort

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

Cardiac 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)

Estimated number of subjects

24000

Study design details

Outcomes

Angioedema is the primary safety event of interest, hypotension, hyperkalemia, hepatotoxicity, and renal impairment are secondary safety events of interest.

Data analysis plan

Demographic and baseline characteristics of patients initiating sacubitril/valsartan or ACEIs will be described using contingency tables for categorical variables and mean, SD, range, median and IQR for continuous variables in each database. The risk of the outcomes of interest will be assessed as incidence rates (IRs) along with 95% confidence intervals (CIs) in users of sacubitril/valsartan and ACEIs. Exploratory: Adjusted relative risks of angioedema will be estimated as hazard ratios (HRs) with 95% CIs among new users of sacubitril/valsartan, (a) who are treatment-naïve to ACEIs and ARBs, and (b) separately, in LCZ696 initiators regardless of prior ACEI or ARB use, relative to new users of ACEIs (treatment-naïve to ACEIs) by using Cox regression models.

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