NOVARTIS

Quantitative Safety and Epidemiology

Non-Interventional Study Protocol (PASS) with secondary use of data

REDACTED PROTOCOL

LCZ696B2014

Title	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
Protocol version identifier	v01.1 – first amendment
Date of last version of protocol	22-March-2022
EU PAS register number	EUPAS18214 (http://www.encepp.eu/encepp/viewResource.htm?id=18809)
Active substance	Sacubitril/valsartan (LCZ696) ATC code: C09DX04
Medicinal product	Entresto®
Product reference	EMEA/H/C/004062
Procedure number	EMEA/H/C/004062/MEA/002
Name of Marketing authorization holder(s)	Novartis Europharm Limited
Joint PASS	No

Research question and objectives	With this non-interventional study, real-world data will be gathered on the risk of angioedema and other potential or identified risks (as listed in the Entresto® Risk Management Plan) associated with LCZ696 as compared to ACE inhibitors in adult patients with heart failure
Country (-ies) of study	Denmark, Germany, Italy, the Netherlands, Spain, United Kingdom
Author	[redacted]

[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
MAH contact person	[redacted]

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List of abbreviations

ACE(I)	Angiotensin Converting Enzyme (Inhibitor)
ADM	Administrative
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
ARS	Agenzia Regionale di Sanità della Toscana
ATC	Anatomical Therapeutic Chemical
BIPS	Leibniz Institute for Prevention Research and Epidemiology – BIPS (formerly Bremer Institut für Präventionsforschung und Sozialmedizin)
BMI	Body Mass Index
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease – 2019
CPRD	Clinical Practice Research Datalink
CRO	Contract Research Organization
Db	Database
DE	Germany
DK	Denmark
EMA	European Medicines Agency
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ES	Spain
EU	European Union
FNR	False negative rate
GePaRD	German Pharmacoepidemiological Research Database
GM	German Modification
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
HES	Hospital Episode Statistics
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSD	Health Search Database
ICD-9	The International Classification of Diseases, 9th Revision
ICD-10	The International Classification of Diseases, 10th Revision
ICPC	International Classification of Primary Care
IQR	Interquartile Range
IR	Incidence Rate
IT	Italy

LBQ657	The active metabolite of the prodrug sacubitril
LCZ696	Sacubitril/valsartan
MRA	Mineralocorticoid Receptor Antagonist
NEP	Neutral Endopeptidase
NHS	National Health Service
NIS	Non-Interventional Study
NL	The Netherlands
NLP	Natural Language Processing
NSAID	Non-Steroid Anti-Inflammatory Drug
NYHA	New York Heart Classification
OTC	Over the Counter
PSOW	Propensity Score Overlap Weight
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PASS	Post-Authorization Safety Study
PI	Principal Investigator
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
PY	Patient-Year
R	R programming language
RAAS	Renin-Angiotensin-Aldosterone System
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
RR	Relative Risk
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software package from SAS Institute Inc.
SD	Standard Deviation
SHI	Statutory Health Insurance
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SMD	Standardized Mean Difference
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient Ischemic Attack
UK	United Kingdom
ULN	Upper Limit of Normal
UMLS	Unified Medical Language System
US	United States
WCIA	Werkgroep Coördinatie Informatisering en Automatisering
WHO	World Health Organization

1 Responsible parties

Table 1-1 Main responsible parties

Role	Person
[redacted]	

2 Abstract

Title

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.

Version and date

v01.1 (Update of Amendment 1) – 22-Mar-2022

Name and affiliation of main author

[redacted]

Rationale and background

LCZ696 (sacubitril/valsartan; ATC code C09DX04; Entresto®) exhibits a novel mechanism of action to treat heart failure (HF) with the angiotensin receptor neprilysin inhibitor (ARNI) 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) on 19 November 2015. In the EU, Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

As agreed with the Committee for Medicinal Products for Human Use (CHMP), Novartis will conduct a non-imposed non-interventional Post-Authorization Safety Study (PASS; category 3) for the risk of angioedema in association with sacubitril/valsartan use. In addition to the risk of angioedema, this study will investigate the risks of hypotension, hyperkalemia, hepatotoxicity, and renal impairment (all included in the Risk Management Plan [RMP] for Entresto as 'important identified risks', except 'hepatotoxicity' which is listed as 'important potential risk').

Research question and objectives

This non-interventional study aims to estimate the risk for angioedema associated with use of sacubitril/valsartan, as well as the risks for hypotension, hyperkalemia, hepatotoxicity, and renal impairment, compared to use of angiotensin converting enzyme inhibitors (ACEIs) in adult patients with HF.

The objectives of the study are:

Primary objective

1. To estimate the incidence of specific safety events of interest in HF patients newly starting treatment with sacubitril/valsartan (regardless of prior use of ACEIs or angiotensin II receptor blockers (ARBs))
2. To estimate the incidence of all specific safety events in HF patients newly starting treatment with sacubitril/valsartan without prior exposure to ACEIs or ARBs

The primary safety event of interest is:

- Angioedema

Secondary events of interest are:

- Hypotension
- Hyperkalemia
- Hepatotoxicity
- Renal impairment

Secondary objectives:

1. To estimate the incidence of angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment in adult HF patients newly starting treatment with ACEIs (patients without prior exposure to ACEIs/ARBs)
2. To estimate the incidence of angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment in adult HF patients with ACEI exposure (regardless of prior use of ACEIs/ARBs)

Exploratory objectives:

1. To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (without prior ACEI/ARB exposure) as compared to adult HF patients newly starting treatment with ACEIs (without prior ACEI/ARB exposure)
2. To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior ACEI/ARB exposure) versus adult HF patients newly starting treatment with ACEIs (without prior ACEI/ARB exposure)
3. To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior ACEI/ARB exposure) vs. HF patients with ACEI exposure (regardless of prior ACEI/ARB exposure)

Study design

Cohort study to estimate the incidence and relative risks for angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment in adult patients diagnosed with HF (prevalent and incident) newly starting sacubitril/valsartan or using ACEIs.

Population

The overall study population will consist of adult patients (≥ 18 years of age) with prevalent or incident HF initiating either sacubitril/valsartan or using an ACEI (no concomitant use of sacubitril/valsartan and ACEI) during the study period, identified from seven European electronic healthcare databases from 6 countries: Germany (DE), Denmark (DK), the Netherlands (NL), Italy (IT), Spain (ES), and the United Kingdom (UK). Stratifications will be made for prior use of ACEIs/ARBs.

For each database, the study period starts at the time Entresto® (sacubitril/valsartan) was launched in the country. The end of the study period will be June 2021 at the latest.

Variables

The primary outcome of interest is angioedema. In addition, hypotension, hyperkalemia, hepatotoxicity, and renal impairment will be studied. These events will be identified, using the database specific coding systems, e.g., Read, International Classification of Diseases (ICD) 9th or 10th revision, Clinical Modification (ICD-9/-10 CM), ICD-10 German Modification (GM), or International Classification of Primary Care (ICPC), the latter supplemented with natural language processing.

The exposures of interest are new treatment with sacubitril/valsartan or an ACEI. Patients must have a recorded diagnosis of HF prior to or within three months (90 days) after the first prescription (or pharmacy fill) of sacubitril/valsartan or an ACEI. Any ACEIs used in the countries covered by the databases during the study time period will be included. Patients will be considered ACEI/ARB-naïve (incident, or new users) if they have not been prescribed an ACEI/ARB within the 365 days before the index date.

We will capture information on potential confounders such as patient demographics/characteristics, comorbidities, and concomitant medications at the index date or during a minimal 365-day look-back period before the index date.

Data sources

All data will be obtained from seven European electronic healthcare databases:

- Aarhus (*Aarhus University Prescription Database and Danish National Patient Registry*) from Denmark
- ARS (*Agenzia Regionale di Sanità della Toscana*) from Italy
- CPRD (*The Clinical Practice Research Datalink*) from the UK
- GePaRD (*German Pharmacoepidemiological Research Database*) from Germany
- HSD (*Health Search IMS Health Longitudinal Patient Database*) from Italy
- PHARMO (*The PHARMO Database Network*) from the Netherlands
- SIDIAP (*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària*) from Catalonia, Spain

Study size

Based on estimates from forecasts, approximately 29,000 sacubitril/valsartan initiators may be included in this study with an accumulated 24,000 patient-years (PYs) of sacubitril/valsartan exposure. If 132 cases of angioedema are reported, this would allow estimating an incidence rate (IR) of 5.5/1,000 PYs with a 95% confidence interval (CI) ranging from 4.6 to 6.5. Feasibility assessments will provide information about how many potential patients initiating ACEIs will possibly be included in the study.

Data analysis

Descriptive statistics will be provided as applicable, and IRs will be estimated using Poisson regression. Cox regression models will only be used to estimate adjusted relative risks for the exploratory analyses on angioedema. Cumulative incidence curves will be provided for the outcome of angioedema.

Milestones

Start of data collection: Q2 2017

End of data collection: After reaching approximately 24,000 PYs of total exposure with sacubitril/valsartan in the database(s), but 31 December 2021 at the latest.

Interim report 1: submitted Q1 2018

Interim report 2: submitted Q1 2019

Interim report 3: submitted Q1 2020

Interim report 4: submitted Q1 2021

Interim report 5: Q1 2022

Registration in the EU PAS register: 16 March 2017

Final report of study results: expected on 31 December 2022

3 Amendments and updates

Amendment 1.1 Update

Amendment 1.1 rationale

Following the endorsement of Amendment 1 by the PRAC/CHMP in January 2022, this update to the protocol amendment 01 addresses PRAC's comments raised in the final assessment report as detailed in Table 3-1 below.

Changes to specific sections of this amended protocol are shown in the track change version using ~~strike-through red font for deletions~~ and red underline for insertions.

Amendment 1

Amendment rationale

The first interim report of LCZ696B2014 submitted to PRAC in March 2018, including data through December 2016, identified a total of 250 initiators of sacubitril/valsartan (regardless of prior ACEI/ARB use) fulfilling the inclusion criteria [redacted]. In the second interim report, and as part of the ongoing feasibility analyses, ARS data from Italy were included to complement the original five databases [redacted] The third [redacted] and fourth interim report [redacted] in addition to ARS, included GePaRD data. These two additional databases were considered crucial to reach the expected sample size of 24,000 patient-years (PYs) at the planned end of data collection (December 2021). In addition, based on the results from the feasibility analyses [redacted] these data were considered to be of sufficient quality by Novartis to be added to the original five databases. This was confirmed by PRAC in their response in March 2021. The addition of these two databases is the main rationale triggering this protocol amendment. Furthermore, divergent from the initial LCZ696B2014 protocol v00 [redacted] all analyses will be performed in collaboration between the principal investigator (PI), as scientific lead, and the PHARMO Institute for Drug Outcomes Research. [redacted]

Other (substantial) amendments or updates to the original LCZ696B2014 protocol version 00 [redacted] are detailed below in Table 3-1.

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
Amendment v01				
1	09-Sep-2021	Various sections throughout the protocol	Amendment	ARS and GePaRD added to complement the five original databases
2	09-Sep-2021	Title page	Update	Addition of the EUPAS number
3	09-Sep-2021	Title page	Update	Updated affiliation and address of PI
4	09-Sep-2021	Section 1, Table 1-1	Update	Update of contact information of the main responsible parties
5	09-Sep-2021	Section 4, Table 4-1	Update	Milestone table was updated with an additional column on 'Actual dates'
6	09-Sep-2021	Section 5	Update	Additional, more recent references added

Number	Date	Section of study protocol	Amendment or update	Reason
7	09-Sep-2021	Section 6.3	Update	Order of exploratory objectives was altered, as the naïve sacubitril/valsartan cohort was deemed underpowered and should not be considered the primary exploratory analysis
8	09-Sep-2021	Section 7.2.1	Amendment	Databases from which the source populations are identified were expanded to include ARS and GePaRD
9	09-Sep-2021	Section 7.2.3, Table 7-1	Update	Table 7-1 was expanded to also include the expected end of data availability and the duration of the study period by database
10	09-Sep-2021	Section 7.2.4 Exclusion criteria	Amendment	Patients with a prescription (or pharmacy fill) for sacubitril/valsartan and ACEIs on the same day were added as an exclusion criterion For the safety event of hepatotoxicity the exclusion of chronic hepatic conditions was extended with hepatotoxic events of specific etiology prior to index date
11	09-Sep-2021	Section 7.2.5	Update	A minimal look-back period of 365 days is applied because a fixed period is insufficient to capture chronic morbidity in all databases
12	09-Sep-2021	Section 7.3.1.2	Amendment	The exposure group of historical ACEI users (naïve to prior ACEI/ARB) was deleted as the 4th interim showed that cohort 4 is large enough and that there is no need for this cohort (former Section 7.3.1.2.3 was deleted)
13	09-Sep-2021	Figure 7-1	Update	Figure 7-1 was replaced by a more detailed figure
14	09-Sep-2021	Table 7-2	Update	Table 7-2 was revised to reflect the changes in the order of the exploratory objectives
15	09-Sep-2021	Section 7.3.2	Update	Clarification that for angioedema a ‘narrow’ (primary) definition is used, and events identified through the mapping terms that would allow identification of hypersensitivity reactions that may indicate angioedema were viewed as a ‘broad’ definition. Separate analysis of the ‘narrow’ definition (primary analysis) and the hypersensitivity reactions (sensitivity analysis) will be performed. Validation of the hypersensitivity reactions will inform possible underestimation of angioedema events.

Number	Date	Section of study protocol	Amendment or update	Reason
16	09-Sep-2021	Section 7.3.2	Update	Clarification of the definition of angioedema and hypotension that will be used. Angioedema includes the 'narrow' definition (primary) and hypersensitivity reactions (sensitivity) The definition of hypotension includes a 'narrow' (primary) and 'broad' (sensitivity analysis) definition.
17	09-Sep-2021	Section 7.3.3	Update	List of comedications and comorbid conditions was updated, as was the proxy used for estimating HF severity and overall health status of the patient
18	09-Sep-2021	Section 7.4	Amendment	Subsections added to cover for ARS and GePaRD as additional databases
19	09-Sep-2021	Section 7.6	Amendment	Data management section revised to reflect the process applied by PHARMO
20	09-Sep-2021	Section 7.7.1.2.2	Amendment	The primary analysis of all objectives will be censored at 31 December 2019, i.e. limited to the pre-COVID period. Databases with partial linkage to hospitalization data will be analyzed stratified by the linkage for all objectives The method of handling confounding by propensity score adjustment was specified
21	09-Sep-2021	Section 7.7.1.2.3	Amendment	The sensitivity analyses of sacubitril/valsartan misclassification and ethnicity were deleted, based on feasibility assessments showing that these were not possible. However, ethnicity will be included in the propensity score model for CPRD, including the missing values as a separate category Sensitivity analysis of the full study period (end of data availability) was added.
22	09-Sep-2021	Section 7.8	Update	Additional information added on operating procedures and quality control
23	09-Sep-2021	Section 7.9	Update	Limitations updated to reflect latest insights
24	09-Sep-2021	Section 7.10	Update	Other aspects updated to reflect latest insights
Amendment v01.1				
25	22-Mar-2022	Section 6.3	Update	Reverted order of exploratory objectives to initial order
26	22-Mar-2022	Section 7.1.2	Update	Summary of feasibility assessments added
27	22-Mar-2022	Table 7-2	Update	Table updated to reflect reverted order of exploratory objectives

4 Milestones

Table 4-1 PASS Study milestones

Milestone	Planned date	Actual date
Start of data collection	Q2 2017	September 2017
End of data collection	After reaching approximately 24,000 PYs of total exposure with sacubitril/valsartan in the database(s), but latest 31 Dec 2021	NA
Interim report 1	Q1 2018	Submitted March 2018
Interim report 2	Q1 2019	Submitted March 2019
Interim report 3	Q1 2020	Submitted March 2020
Interim report 4	Q1 2021	Submitted March 2021
Interim report 5	Q1 2022	NA
Registration in the EU PAS register	After endorsement by CHMP/PRAC	16 March 2017
Final report of study results	31 December 2022	NA

5 Rationale and background

Sacubitril/valsartan (active substances sacubitril and valsartan, ATC code C09DX04; product name Entresto®) exhibits a novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) 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. The complementary cardiovascular benefits of sacubitril/valsartan in HF patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan (Vardeny et al 2014).

In the main randomized controlled trial conducted for sacubitril/valsartan (the PARADIGM-HF trial) which included more than 8,400 HF patients with New York Heart Association (NYHA) class II-IV (ejection fraction $\leq$ 40%), sacubitril/valsartan significantly reduced cardiovascular mortality and the risk of hospitalization by approximately 20%. It also significantly decreased the symptoms and physical limitations associated with HF compared to treatment with the ACEI enalapril, while showing a similar safety profile (McMurray et al 2014).

Based on this pivotal trial, sacubitril/valsartan (Entresto®) was approved in 2015 in the United States (US), the EU and various other countries. In the EU, sacubitril/valsartan (Entresto®) is approved for the treatment of adult patients with symptomatic chronic heart failure and a reduced ejection fraction.

This study aims to assess the risk for angioedema associated with sacubitril/valsartan in a real-world setting, as well as the risk for several other important identified or potential risks currently listed in the Entresto® Risk Management Plan (RMP) including hypotension, hyperkalemia, hepatotoxicity, and renal impairment.

5.1 Angioedema

The majority of data on the risk for angioedema with sacubitril/valsartan was obtained from the PARADIGM-HF trial. The design of this trial entailed three phases: 1) a single-blind run-in

period during which all patients received enalapril, followed by 2) a single-blind run-in period during which all patients received sacubitril/valsartan, and 3) a double-blind treatment phase in which subjects were randomized to either of the study groups (enalapril vs. sacubitril/valsartan). Patients with a history of angioedema were excluded from the trial. In the PARADIGM-HF trial, angioedema was blindly adjudicated as an outcome of specific interest. Overall, during the enalapril run-in period there were 15 patients (0.14%) with confirmed angioedema events, and during the sacubitril/valsartan run-in, 10 patients (0.11%) had adjudication committee-confirmed angioedema events in association with sacubitril/valsartan.

Confirmed angioedema occurred during the double-blind period in 19 patients (0.45%) in the sacubitril/valsartan treated group (n=4,203) and in 10 patients (0.24%) in the enalapril treated group (n=4,229). Although there were slightly higher rates of angioedema reported for sacubitril/valsartan in the double-blind period, there were no severe cases of angioedema involving airway compromise or requiring mechanical support. A higher incidence of angioedema was observed in Black patients treated with sacubitril/valsartan (2.4%) versus enalapril (0.5%) although the number of Black patients in PARADIGM-HF was small. Racial differences in the risk for developing angioedema are well known for ACEIs (Brown et al 1996, Kostis et al 2005, Miller et al 2008, Makani et al 2012, Reichman et al 2017).

In a meta-analysis including five randomized controlled trials with a total of 14,841 patients exposed to sacubitril/valsartan with follow-up ranging from 2 to 27 months, the collective percentage of angioedema was 0.5% in the sacubitril/valsartan arms versus 0.3% in the control arms (ACEIs/ARBs) (pooled odds ratio of 1.35; 95% confidence interval (CI): 0.45 to 4.1; p = 0.59) (Dani et al 2021). An additional recent systematic review and meta-analysis of randomized controlled trials (RCTs) did not find an increased angioedema risk of sacubitril/valsartan versus active control treatment overall (risk ratio: 1.72 [95% CI: 0.93-3.18] based on 15 RCTs), nor when compared to ACEIs (risk ratio: 0.87 [95% CI: 0.21-3.59] based on four RCTs) (Martins et al 2021).

The risk for angioedema associated with sacubitril/valsartan in every-day clinical practice is currently unknown and will be investigated in this non-interventional study. Based on the fourth interim analysis of study LCZ696B2014, the crude pooled IR of angioedema in association with use of sacubitril/valsartan (regardless of prior ACEI/ARB use) was of similar magnitude compared to ACEIs users treatment-naïve to ACEIs/ARBs) (i.e., 0.7 [95% CI: 0.4-1.1] per 1,000 PYs versus 1.0 [95% CI: 0.9-1.2] per 1,000 PYs) ([redacted]

Angioedema is included in the Entresto® RMP as an identified risk.

5.1.1 Angioedema risks associated with use of other neprilysin-inhibitors

Sacubitril is a neprilysin-inhibitor. Neprilysin (also known as 'neutral endopeptidase' [NEP]) increases levels of bradykinin, which is associated with angioedema and may have an important causal role. Studies with omapatrilat – an antihypertensive agent that has both NEP- and ACE-inhibiting properties – demonstrated that dual ACE- and neprilysin-inhibition increased the risk for serious angioedema (Kostis et al 2004) probably by inhibiting all three enzymes responsible for the breakdown of bradykinin (ACE, NEP, and aminopeptidase P) (Fryer et al 2008). Unlike omapatrilat, sacubitril's active metabolite LBQ657 is a selective NEP-inhibitor and blocks only one of these three enzymes. The other active substance of sacubitril/valsartan, the ARB

valsartan is known to have a lower risk of angioedema compared to ACEIs (Fryer et al 2008, Toh et al 2012).

5.1.2 Angioedema risks associated with use of ACE-inhibitors

The overall IR of angioedema experienced by ACEIs users reported in non-interventional studies (NIS) ranges from 1.6 to 4.4 per 1,000 PYs, with the incidence being highest directly after treatment initiation (Brown et al 1996, Burkhart et al 1996, Miller et al 2008, Toh et al 2012, Reichman et al 2017, Pannozzo et al 2018). In about 50% of cases, angioedema occurs in the first week of ACEI use (Slater et al 1988, Sabroe and Black 1997, Malde et al 2007). Toh et al (2012) and Reichman et al (2017) showed that the angioedema IR for ACEIs can be around 9.7 to 11.3 per 1,000 PYs in the first 30 days of follow-up after ACEI treatment start, reach 3.8 per 1,000 PYs during the second month of follow-up, and decrease to approximately 2.6 per 1,000 PYs after 6-12 months (Toh et al 2012). Miller et al (2008) found that the incidence of ACEI-associated angioedema was higher in older subjects, those with chronic HF or coronary artery disease, and confirmed the higher risk in African American and female subjects while the risk of ACEI-associated angioedema was lower in patients with diabetes mellitus. The clinical trial by Kostis et al (2005), found that seasonal allergies and a history of drug-related rash were independent risk factors for ACEI-associated angioedema.

All of these studies, however, reflect ACEI use predominantly for hypertension and not specifically for HF – which itself may constitute a greater risk for angioedema (Miller et al 2008, Makani et al 2012).

5.2 Hypotension

In the double-blind period of the PARADIGM-HF trial, hypotension and clinically relevant low systolic blood pressure (<90 mmHg and decrease from baseline of >20 mmHg) were reported in 17.6% and 4.8% of sacubitril/valsartan treated patients compared to 11.9% and 2.7% of enalapril treated patients, respectively, with hypotension reported as a serious adverse event (AE) in approximately 1.5% of patients in both treatment arms. Hypotension was more commonly reported for patients >65 years old, and those with renal disease. A recent systematic review and meta-analysis of RCTs identified a significantly increased risk of hypotension of sacubitril/valsartan versus active control treatment (risk ratio: 1.45 [95% CI: 1.27-1.67] based on 13 RCTs) and a risk increase of similar magnitude when compared to ACEIs (risk ratio: 1.49 [95% CI: 1.15-1.95] based on five RCTs) (Martins et al 2021).

Hypotension is included in the Entresto® RMP as an identified risk.

Hypotension is often observed in HF patients for whom multiple HF therapies are used, as most of these therapies (i.e., ACEIs/ARBs, β-blockers, mineralocorticoid receptor antagonists [MRAs], diuretics) have blood pressure-lowering effects (Yancy et al 2013). Sacubitril/valsartan also has a blood pressure lowering effect based on its ARB and neprilysin inhibitor properties. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g. those being treated with high doses of diuretics), are at greater risk for hypotension.

5.3 Hyperkalemia

In the double-blind period of the PARADIGM-HF trial, hyperkalemia and serum potassium concentrations >5.4 mmol/l were reported in 11.6% and 19.7% of sacubitril/valsartan – and 14.0% and 21.1% of enalapril-treated patients, respectively. A recent systematic review and meta-analysis of RCTs did not find an increased risk of hyperkalemia of sacubitril/valsartan versus active control treatment overall (risk ratio: 1.09 [95% CI: 0.94-1.27] based on 12 RCTs), nor when compared to ACEIs (risk ratio: 1.16 [95% CI: 0.88-1.54] based on four RCTs) (Martins et al 2021).

Hyperkalemia is included in the Entresto® RMP as an identified risk.

Hyperkalemia may occur with ACEIs, ARBs, and MRA treatment due to blockade of the renin-angiotensin-aldosterone system (RAAS) through inhibition of secretion of aldosterone, particularly in patients who have chronic renal insufficiency (Yancy et al 2013).

5.4 Hepatotoxicity

Clinical data for sacubitril/valsartan do not indicate an overall increased risk for hepatotoxicity, compared to enalapril. In the double-blind period of PARADIGM-HF, 3.3% (n=138) of patients treated with sacubitril/valsartan and 4.4% (n=184) of patients treated with enalapril had adjudicated hepatotoxicity as an AE.

The most frequently reported hepatotoxicity-related events in the sacubitril/valsartan group vs. the enalapril group, respectively, were hepatic steatosis (0.43% vs. 0.50%), ascites (0.36% vs. 0.52%), alanine aminotransferase (ALT) increased (0.31% vs. 0.14%), aspartate aminotransferase (AST) increased (0.31% vs. 0.05%) and International Normalized Ratio (INR) increased (0.26% vs. 0.50%).

Hepatotoxicity is included in the Entresto® RMP as a potential risk.

The limited liver metabolism of sacubitril, LBQ657 and valsartan suggest a low risk of hepatotoxicity. Non-clinical toxicity studies also do not raise concerns with respect to hepatotoxic potential for sacubitril or valsartan. However, given that clinical events of right HF and hypotension may lead to passive liver congestion and hepatic ischemia (Giallourakis et al 2002, van Deursen et al 2010, Ambrosy et al 2012), it is expected that HF patients will have an increased incidence of abnormal liver function or liver related AEs compared to hypertensive patients and the general population.

5.5 Renal impairment

As a consequence of inhibiting the RAAS, decreasing renal function (acute renal failure) may occur in susceptible individuals treated with sacubitril/valsartan. In the double-blind period of PARADIGM-HF, renal impairment was reported in 10.1% of sacubitril/valsartan and 11.5% of enalapril treated patients. A recent systematic review and meta-analysis of RCTs did not find an increased risk of 'acute kidney injury' of sacubitril/valsartan versus active control treatment overall (risk ratio: 0.91 [95% CI: 0.78-1.07] based on eight RCTs), nor when compared to ACEIs (risk ratio: 1.00 [95% CI: 0.79-1.27] based on three RCTs) (Martins et al 2021).

Renal impairment is included in the Entresto® RMP as an identified risk.

Renal impairment occurs in approximately a third of HF patients, which can be further compromised by HF therapies that block the RAAS by decreasing glomerular filtration. However, NEP inhibitors have the potential to increase renal blood flow and provide a renal protective effect (Dries et al 2000, Cao et al 2001, Taal et al 2001). In patients whose renal function depends upon the activity of the RAAS (e.g., patients with severe congestive HF), treatment with ACEIs and ARBs has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and death.

6 Research question and objectives

With this non-interventional study, real-world data will be gathered on the risk of angioedema and other potential or identified risks currently listed in the Entresto® RMP (including hypotension, hyperkalemia, hepatotoxicity, and renal impairment) in association with sacubitril/valsartan versus ACEIs use in adult patients with HF.

6.1 Primary objective

1. To estimate the incidence of specific safety events of interest in HF patients newly starting treatment with sacubitril/valsartan (regardless of prior use of ACEIs or ARBs)

The primary safety event of interest is:

- Angioedema

Secondary events of interest are:

- Hypotension
- Hyperkalemia
- Hepatotoxicity
- Renal impairment

2. To estimate the incidence of all specific safety events (as mentioned above) in HF patients newly starting treatment with sacubitril/valsartan without prior exposure to ACEIs or ARBs

6.2 Secondary objectives

1. To estimate the incidence of angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment in adult HF patients newly starting treatment with ACEIs (patients without prior exposure of ACEIs/ARBs)
2. To estimate the incidence of angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment in adult HF patients with ACEI exposure (regardless of prior use of ACEIs or ARBs)

6.3 Exploratory objectives

1. To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (without prior ACEI/ARB exposure) as compared to adult HF patients newly starting treatment with ACEIs (without prior ACEI/ARB exposure)

2. To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior ACEI/ARB exposure) versus adult HF patients newly starting treatment with ACEIs (without prior ACEI/ARB exposure)
3. To estimate the relative risk of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan (regardless of prior ACEI/ARB exposure) versus adult HF patients with ACEI exposure (regardless of prior ACEI/ARB exposure)

All comparative analyses in this study are considered exploratory due to potential biases that exist related to selecting patients on ACEI treatment who are either treatment-naïve to ACEIs and ARBs or are prevalent ACEI users as our comparator group (see also Section 7.1.1 and Section 7.9).

7 Research methods

7.1 Study design

This is 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 separately as prevalent users); see Section 7.3.1 for more details on exposure cohort classifications.

7.1.1 Rationale for study design

To obtain a robust estimate of the incidence of angioedema – the primary safety event of interest – as well as of the other safety events (i.e. hypotension, hyperkalemia, hepatotoxicity, and renal impairment) in patients newly starting sacubitril/valsartan (incident users), an initial cohort of all sacubitril/valsartan initiators will be identified (regardless of prior exposure to ACEIs or ARBs) with patient accrual beginning at the specific launch date of sacubitril/valsartan (see Table 7-1) in those EU countries from which healthcare database information will be used for this study (see Section 7.4 'Data sources'). In addition, an initial contemporaneous comparator cohort of ACEIs initiators will be identified. Data collection will end when the necessary sample size of 24,000 PYs is reached (see Section 7.5 'Study size/power calculation'), but on 31 December 2021 at the latest (even when the target sample size is not reached).

A new user design (Ray 2003, Food and Drug Administration 2013, Yoshida et al 2015) is proposed to minimize the risk of a prevalent user bias and depletion of susceptibles. This is of particular importance for ACEIs users. Sacubitril/valsartan was newly introduced to the market and the cohort of users therefore automatically consists of new users. As indicated in the sacubitril/valsartan 'Summary of Product Characteristics' (SmPC), it is contraindicated for patients with a known history of angioedema related to previous ACEI or ARB therapy, or with hereditary or idiopathic angioedema. The combination of sacubitril/valsartan with an ACEI is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated within 36 hours after taking the last dose of ACEI therapy.

Since the majority of sacubitril/valsartan users are expected to have been treated with an ACEI or ARB before starting sacubitril/valsartan, these patients will likely have a lower baseline risk of angioedema as susceptible patients have been depleted. ACEI initiators who are treatment

naïve to ACEIs and ARBs however, will likely have a higher baseline risk of angioedema since this population includes all patients who are susceptible to an angioedema event.

As the risk of ACEI-associated angioedema is highest very shortly after treatment initiation and decreases over time (Kostis et al 2005, Miller et al 2008, Toh et al 2012), a cohort of prevalent ACEI users would be biased towards a lower angioedema risk compared to ACEI naïve patients. The majority of patients experiencing angioedema while treated with ACEIs can be expected to discontinue ACEI treatment and would therefore unlikely be part of a prevalent ACEI user cohort. Thus, comparing sacubitril/valsartan initiators regardless of their prior exposure to ACEIs/ARBs, to ACEI initiators who are treatment naïve to ACEIs and ARBs is likely to bias the comparative (explorative) analysis in favor of sacubitril/valsartan. Therefore, it is considered that the optimal comparison is between sacubitril/valsartan initiators who are treatment naïve to ACEIs/ARBs and ACEI initiators without prior ACEIs/ARB use. To provide an estimate of what may happen if prevalent users are included, we will explore all these analyses (see Section 6.3 Exploratory objectives).

Accruing the required sample size for the comparison of patients initiating sacubitril/valsartan treatment without prior ACEI/ARB use with those newly initiating treatment with ACEIs/ARBs within the proposed timelines will be very unlikely. It should be expected that many HF patients (both prevalent and incident) will have been previously exposed to an ACEI used as treatment for hypertension or other comorbid diseases prevalent in HF patients (e.g., acute myocardial infarction, diabetic nephropathy). A US study in patients with incident HF diagnosed between 2005 and 2008 from four sites participating in the Cardiovascular Research Network (CVRN) found an exposure prevalence to ACEIs or ARBs in patients with incident HFrEF (n=3,941, mean age 69 years) of 43% (Goldberg et al 2013). In the European 'ESC-HF Long-Term Registry' a prospective cohort study with primary data collection, including over 7,400 patients with prevalent chronic HF (median age 66 years) were enrolled over two years. In the subgroup of patients with HFrEF (n=4,792), 92.2% were treated with ACEIs or ARBs at baseline (Maggioni et al 2013). Thus, indicating that the absolute number of ACEI initiators who are treatment naïve to ACEIs and ARBs will be limited. If necessary, it was initially planned to supplement the contemporaneous comparator cohort with a historical cohort of ACEI initiators who are treatment naïve to ACEIs using data prior to Entresto® market approval if needed. However, the most recent interim report for the LCZ696B2014 study identified a total of 116,041 ACEI initiators being treatment naïve to ACEIs/ARBs [redacted] when both ARS and GePaRD were included. Based on these results, inclusion of a historical cohort of ACEI initiators treatment naïve to ACEIs/ARBs does not seem necessary.

In addition, to explore the impact of depletion of susceptibles we will assess the rate of events in users of ACEIs with prior use of ACEIs/ARBs.

7.1.2 Feasibility assessments

The following feasibility assessments were conducted to inform the design of the study and to provide information on its limitations:

1. To describe the numbers and characteristics of ACEIs users over time (annually; 2011 to most recent year available for each data partner), stratifying users into those who are treatment-naïve and non-naive to ACEIs and ARBs, and estimate standardized differences in characteristics over time

2. To investigate the potential gap in available sacubitril/valsartan prescriptions (or pharmacy fills) due to specialist prescribing in or outside the hospital, and its potential impact on the objectives of the study LCZ696B2014, especially at treatment initiation in the different databases
3. To assess event rates in the general adult population of the safety outcomes of angioedema, hypotension, hyperkalemia, hepatotoxicity, and renal impairment based on different algorithms for the LCZ696B2014 study, and to harmonize the codes used to detect these outcomes across the various databases
4. To assess how each database can best assess the severity of HF
5. To assess the indication of sacubitril/valsartan users without recorded HF diagnosis

A high-level summary of the feasibility results for each objective relevant for study LCZ696B2014 is provided below (for more details, see [redacted]):

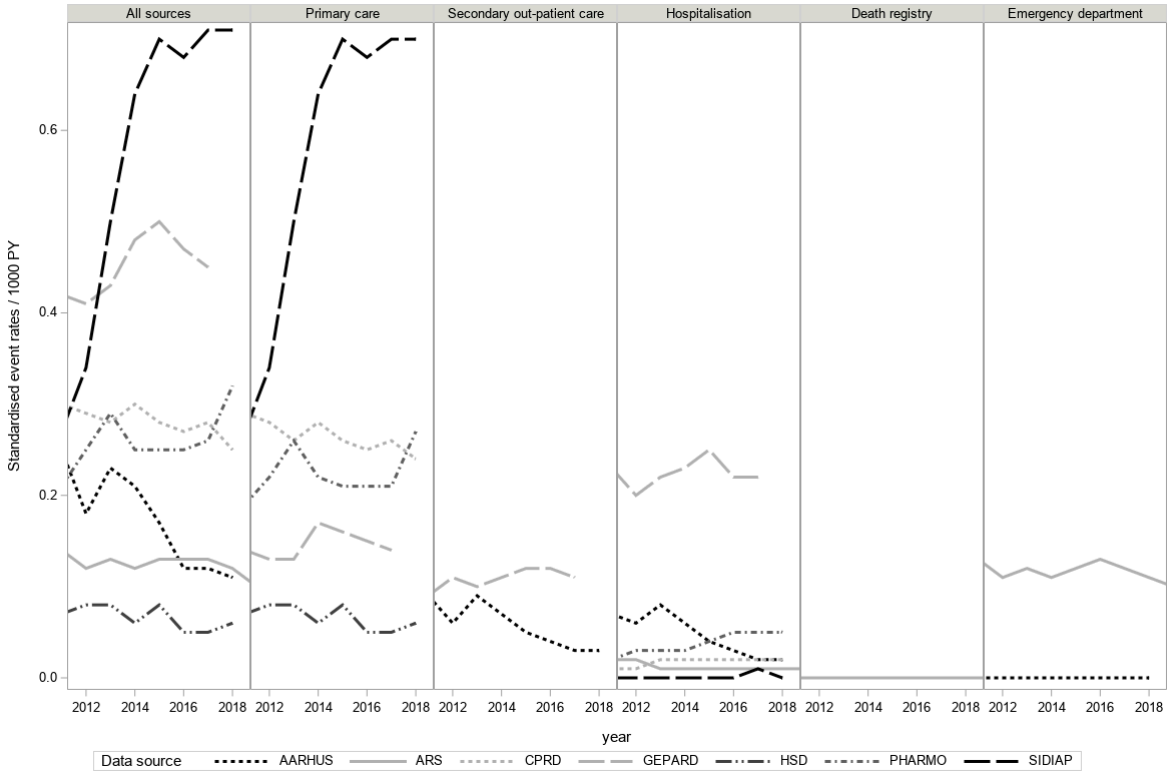
Ad objective 1: No major differences were observed in the characteristics of ACEI users before and after launch of sacubitril/valsartan, indicating that ACEI users from the period before launch could be included as a historical ACEI cohort to complement contemporaneous ACEI initiators. However, the fourth interim report of the LCZ696B2014 study identified >89,000 HF patients in "ACEI cohort 3" (ACEIs users regardless of prior ACEI/ARB use [i.e., mix of prevalent and incident ACEI users]) and almost 567,000 ACEI users when using data from ARS and GePaRD databases. In cohort 4 (ACEIs users without prior use of ACEIs/ARBs [i.e., treatment-naïve ACEI users]) >21,500 HF patients were identified and >116,000 HF patients when data from ARS and GePaRD was included. As this number will further increase until the final LCZ696B2014 analyses, an addition of historical ACEI users is not required.

Ad objective 2: The potential gap in sacubitril/valsartan prescriptions (or pharmacy fills) due to specialist prescribing in or outside the hospital was assessed by the number of patients with a hospitalization or referral to a specialist in the 3 months prior to the index date. A substantial proportion of sacubitril/valsartan users included in the feasibility study cohort were in specialist/ambulatory care (proportion ranged from 17% in Aarhus to 72% in HSD) or hospitalized within 3 months prior to the first sacubitril/valsartan prescription (proportion ranged from 18% in HSD to 42% in GePaRD). The time between referral or hospitalization for HF and first identified sacubitril/valsartan prescription (or pharmacy fill) in CPRD, HSD, GePaRD, and PHARMO was between 0 and 20 days for most sacubitril/valsartan users. In SIDIAP, this was more than 30 days for most patients. It seems plausible that for a number of these patients the first sacubitril/valsartan prescription may have been missed, either because inpatient prescribing is not present in all databases or outpatient specialist prescriptions are not captured (CPRD, HSD). The impact of misclassification of treatment start cannot be assessed with sensitivity analyses, because patients with an angioedema event during treatment that is not captured, will not have subsequent out-patient prescription records for sacubitril/valsartan that are captured, and therefore will not be included in the sacubitril/valsartan cohorts. If initiation of sacubitril/valsartan use is missed, but later exposure is captured, exposure time will be slightly underestimated and safety event rates may be slightly overestimated.

Ad objective 3: Crude and age-/sex-standardized event rates were calculated for the safety events of interest in the general (adult) database population and were compared across databases overall and by data provenance.

As an example, Figure 7-1 displays the assessment of safety event rates for angioedema (‘*narrow*' definition).

Figure 7-1 Age- and sex-standardized safety event rates of angioedema (‘*narrow*’) in a general adult population by provenance over time



Results suggest that all databases are able to capture the safety events of interest. The extent to which each safety event is captured differs per database and depends on the setting in which the data were captured (primary or secondary care), the granularity of the corresponding coding system(s), and the organization of healthcare in each country. For GePaRD, 12 algorithms for the confirmation of recorded diagnoses were tested and evaluated. Table 12-1 includes the final choice of algorithm made by GePaRD after discussion with both investigators and German physicians with knowledge of the healthcare system and recording practices. For angioedema, an algorithm of one discharge diagnosis (main or secondary) or two outpatient diagnoses from different physicians within up to three months was considered to be the most reliable algorithm for a confirmed diagnosis of angioedema.

Code harmonization for the safety events of interest resulted in exclusion of unspecific diagnoses and differentiation of ‘*narrow*’ and ‘*broad*’ diagnosis definitions for angioedema and hypotension, to allow exploration of specificity and sensitivity of captured results in the final analysis for study LCZ696B2014. The specificity of all safety events of interest based on the harmonize code list are further examined in a validation study.

Ad objective 4: Of 5,185 adult sacubitril/valsartan initiators with recorded HF diagnosis and sufficient history and follow-up identified across the seven databases, GePaRD contributed

most sacubitril/valsartan initiators (N=4,724) [redacted]. Whereas GePaRD, ARS, and PHARMO cannot provide any information on HF severity. HSD and SIDIAP captured information on left ventricular ejection fraction (LVEF), and Aarhus, CPRD, HSD, and SIDIAP captured information on NYHA classification. However, all information of HF severity is only available for a relatively small proportion of patients in each database (10-20%). HSD and SIDIAP also captured information on HF phenotype. For HF treatment, only the number of medications is recorded in all databases whereas the dose is not captured at the same level of detail. The number of drug classes used in the treatment of HF could be a good overall measure of HF severity and would be possible to be included as proxy for HF severity.

Any effect of the severity of HF in relation to the safety events of interest in the LCZ696B2014 study (in particular with respect to angioedema) is expected to be marginal, and likely to be mediated through comedication use rather than ejection fraction per se.

Ad objective 5: A patient profile review was performed to assess the putative alternative indication of sacubitril/valsartan users without recorded HF diagnosis. The review showed that alternative cardiac diagnoses such as coronary artery disease, myocardial infarction and heart arrhythmias were found in the majority of sacubitril/valsartan users without a recorded HF diagnosis. In addition, due to the reimbursement conditions for sacubitril/valsartan it is likely that HF was present although not recorded separately from the underlying cardiovascular disease. Sensitivity analyses of all sacubitril/valsartan users regardless of a recorded HF diagnosis record were conducted as part of the third and fourth interim reports of study LCZ696B2014. No differences in IRs for any safety event were observed when compared to IRs for all sacubitril/valsartan users with HF diagnosis. Thus, no sensitivity analysis is planned for the final analysis of the LCZ696B2014 study.

7.2 Setting

7.2.1 Source population

The source population for this study will be based on patient-data from seven EU electronic healthcare databases:

- the 'Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) from Catalonia, Spain (ES)
- the 'PHARMO Database Network' (PHARMO) from the Netherlands (NL)
- the 'Health Search IMS Health Longitudinal Patient Database' (HSD) from Italy (IT)
- the 'Aarhus University Prescription Database'(Aarhus) and Danish National Patient Registry from Denmark (DK)
- the Clinical Practice Research Datalink (CPRD) from the United Kingdom (UK)
- the German Pharmacoepidemiological Research Database (GePaRD) from Germany (DE)
- the Agenzia Regionale di Sanità della Toscana (ARS) from IT

7.2.2 Study population

The overall study population will consist of adult patients (≥ 18 years of age) initiating either sacubitril/valsartan or using an ACEI/ARB during the study period and having a recorded

diagnosis of HF in the database prior to or within three months (90 days) after the first prescription (or pharmacy fill) of sacubitril/valsartan or ACEI in the study period.

HF patients will be identified using both recorded inpatient and/or outpatient diagnoses based on the specific coding system used by the individual database (e.g. READ in CPRD, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM) in HSD and ARS, ICD-10 CM in SIDIAP, PHARMO, CPRD (HES), and Aarhus University Prescription Database and the Danish National Patient Registry, ICD-10 German Modification (GM) in GePaRD, and International Classification of Primary Care codes [ICPC] and "Werkgroep Coördinatie Informatisering en Automatisering" codes (WCIA) in PHARMO; see also Table 7-8).

7.2.3 Study period

The study period during which patients can enter the study population will start at the sacubitril/valsartan launch dates in the countries of interest (see launch dates in Table 7-1 below) and will end on the 30th of April 2021 at the latest. The total study time frame (including the beginning of the minimal 365 days look-back period before cohort entry) will begin in December 2014 at the earliest. With a data extraction date in December 2021, the end of data availability will range from December 2019 (GePaRD) through April 2021 (ARS).

Table 7-1 Sacubitril/valsartan launch date in the countries of interest and study duration by database

Country (database)	Launch date	Expected end of data availability	Duration of study period
Aarhus (Denmark)	December 2015	December 2020	61 months
GePaRD (Germany)	January 2016	December 2019	48 months
ARS, HSD (Italy)	April 2016 (reimbursement March 2017)	December 2020 (HSD); April 2021 (ARS)	57 months (HSD); 61 months (ARS)
PHARMO (Netherlands)	July 2016	December 2020	54 months
SIDIAP (Spain)	October 2016	June 2021	57 months
CPRD (United Kingdom)	December 2015	December 2020	61 months

7.2.4 Inclusion and exclusion criteria

Inclusion criteria

Patients will be required to:

- Have initiated sacubitril/valsartan or using an ACEI during the study period
- Be aged ≥ 18 years at the time of the first prescription (or pharmacy fill) for sacubitril/valsartan or an ACEI. If the exact date of birth is not known, January 1st of the calendar year the patient turns 18 years will be the start date when only the year is known, and the first date of the month when the month and the year are known
- Have a recorded diagnosis of HF in the database prior to or within three months (90 days) after the first prescription (or pharmacy fill) of sacubitril/valsartan or ACEI in the study period

- Have ≥ 365 days of valid database history prior to the first prescription (or pharmacy fill) for sacubitril/valsartan or an ACEI (i.e., the patient was registered in the database for at least one year)

Note: In GePaRD, only confirmed diagnoses of HF will be selected by using the following algorithm based on records with a confirmed diagnosis status:

- At least one primary hospital discharge diagnosis of HF
- OR at least two outpatient HF diagnoses

In all cases, the first recorded claims date in the context of a HF diagnosis will be considered as the diagnosis date. In all other databases one diagnosis of HF from in- and/or outpatient registry data or electronic medical records will be used.

Exclusion criteria

- Use of sacubitril/valsartan by patients with prior angioedema history is contraindicated; patients with a recorded angioedema diagnosis prior to index date (see Section 7.2.5 for definition of 'index date') are excluded from all cohorts.
- Patients with concurrent prescriptions or pharmacy fills for sacubitril/valsartan and ACEI (i.e., prescription/pharmacy fill on the same day) will also be excluded and will be reported to reflect violation of the 36-hour washout period of ACEI prior to initiation of sacubitril/valsartan.
- For the assessment of 'hepatotoxicity', we will exclude patients with a hepatotoxic event prior to index date (chronic, acute, viral [including HIV], alcohol- or drug-induced, or codes without defined cause [e.g., "hepatitis unspecified"]. Patients with codes indicating hepatic morbidity suggestive of another etiology ["other specified disorders of liver", biliary or alcohol-induced hepatotoxicity]) before or up to 7 days after the index date will be excluded. This will account for late determination or recording thereof of the excluded etiology of the event.
- Patients with a recorded history of chronic renal disease will be excluded for the assessment of 'renal impairment'.

7.2.5 Cohort start

The date of the first recorded prescription (or pharmacy fill) for sacubitril/valsartan or ACEI in the study period will be defined as the cohort entry (= start of follow-up or 'index date'). A minimal look-back period of 365 days is used to determine baseline characteristics.

7.2.6 Follow-up

Eligible patients will be followed from their cohort entry until the occurrence of the outcome of interest, death, the last date of follow-up available in the data set, or the study end date.

Patients will be censored in the respective cohort if they:

- Had stopped their treatment with sacubitril/valsartan or ACEI
- Added treatment with another renin-angiotensin-aldosterone system (RAAS blocking agent (i.e., add-on of an ACEI [only for initiators of sacubitril/valsartan], an ARB, or aliskiren)

- Switched initial treatment to another RAAS blocking agent (i.e., sacubitril/valsartan to an ACEI, ARB or aliskiren; ACEI to sacubitril/valsartan, an ARB, or aliskiren [switching within the ACEI class, however, was not censored])
- Stopped contributing data to the database (e.g., patient died, or left the practice/health insurance, etc.), whichever will occur first.

See Section 7.3.1 for detailed definitions regarding discontinuation, add-on, or switching.

7.3 Variables

7.3.1 Exposures of interest

Exposures of primary interest are sacubitril/valsartan, ACEIs, and ARBs.

Exposure information will be identified using prescription or pharmacy fill data using the database specific coding system (e.g., Anatomical Therapeutic Chemical [ATC] Classification; British National Formulary [BNF]/Gemscript coding). Any use of ACEIs/ARBs will be included. The duration of each prescription/dispensing will be calculated by dividing the amount by the prescribed dose (if available) and otherwise by the national defined daily dose (DDD) equivalent by the World Health Organization (WHO). Episodes of treatment will be created for sacubitril/valsartan and for ACEIs/ARBs for all prescriptions in the same group if there are less than 90 days between the end of the previous prescription and the start of the new one. Overlap in prescriptions of the same kind will be disregarded (no 'stockpiling').

We will consider patients as ACEI- or ARB-naïve if they do not use an ACEI or ARB recorded within 365 days before the index date, respectively.
We will consider patients as having discontinued treatment if there is a gap in a series of successive prescriptions or pharmacy fills of the index drug class that is ≥90 days after the estimated treatment end of the last prescription or pharmacy fill preceding the gap. The calculated end of the prescription/dispensing will be defined as the date of discontinuation, at which point patients' follow-up time will be censored. In the case where the follow-up ends before the 90 days are over a patient will not be considered to have discontinued.

Four exposure groups (cohorts) will be defined: two for sacubitril/valsartan-, and two for ACEI-users.

7.3.1.1 Sacubitril/valsartan user cohorts

- Sacubitril/valsartan initiators regardless of prior ACEI/ARB use (cohort 1)

This group includes all patients fulfilling the inclusion criteria (Section 7.2.4) and using sacubitril/valsartan during the study period – regardless of prior exposure to ACEIs or ARBs.

- Sacubitril/valsartan initiators treatment naïve to ACEIs/ARBs (cohort 2)

Cohort 2 is the subset of patients from cohort 1- who did not use ACEIs/ARBs in the 365 days prior to the index date.

7.3.1.2 ACEI user cohorts

- ACEIs – users regardless of prior ACEI/ARB use (cohort 3)

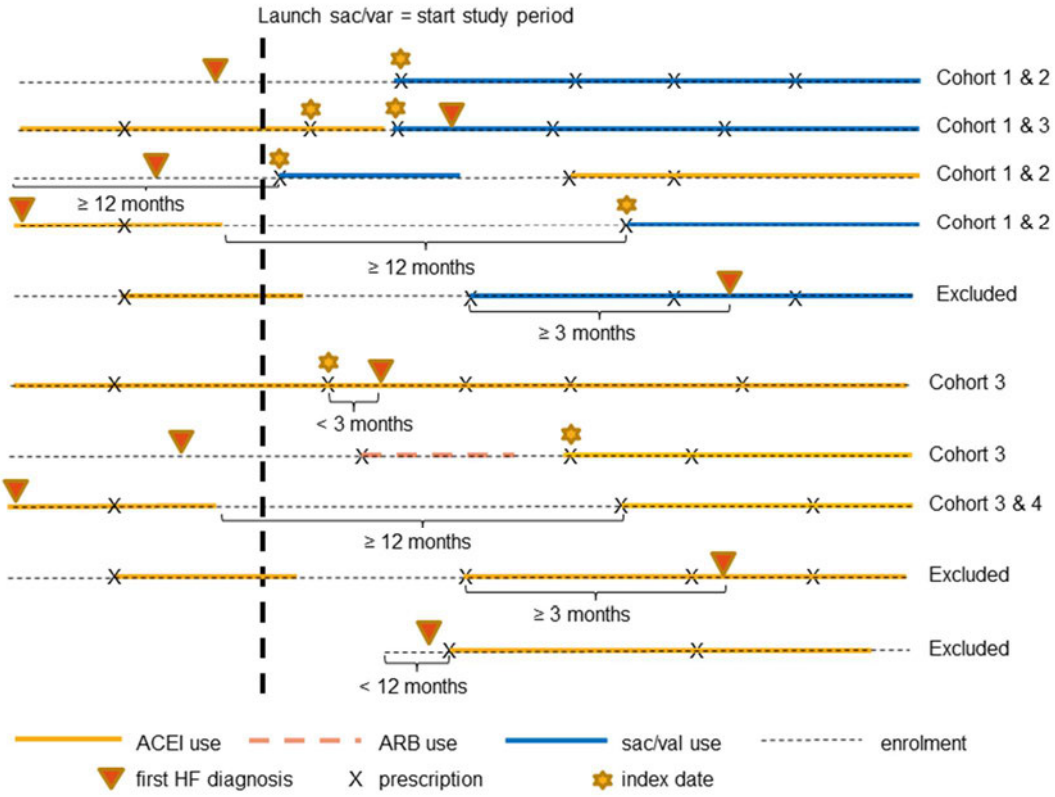
This group includes all patients fulfilling the inclusion criteria (Section 7.2.4) and using ACEIs during the study period – regardless of prior exposure to ACEIs or ARBs. This cohort will be a mix of prevalent and incident ACEI users.

- ACEIs – without prior use of ACEI/ARB - treatment-naïve (cohort 4)

Cohort 4 is the subset of patients from cohort 3. It includes patients who did not use ACEIs/ARBs in the 365 days prior to index date. This sub-cohort corresponds to new ACEIs users - naïve to ACEIs/ARBs.

Note: Patients can be included in more than one cohort. Patients changing from ACEI to sacubitril/valsartan will be included in the corresponding ACEI cohort, as well as the sacubitril/valsartan cohort (only the first change will be considered). Patients changing from sacubitril/valsartan to an ACEI, however, will be censored. Figure 7-2 illustrates cohort allocation and start of follow-up based on various exposure scenarios for sacubitril/valsartan and ACEI users.

Figure 7-2 Cohort allocation based on various exposure scenarios for sacubitril/valsartan and ACEI users



sac/val = sacubitril/valsartan; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; index date = date of first prescription or pharmacy fill of sacubitril/valsartan (cohort 1 & 2) or ACEI use (cohort 3 & 4) (not shown for the excluded patients); HF = heart failure (diagnosis must be recorded at any time prior or within 3 months after index date)

Table 7-2 Study exposure sub cohorts, by study objective

Study objective	Sub cohorts			
	Cohort 1 (any sacubitril/ valsartan)	**Cohort 2 (sacubitril/ valsartan, no prior ACEI/ARB)**	**Cohort 3 (any ACEI)**	**Cohort 4 (ACEI, no prior ACEI/ARB)**
Primary, no 1 (IRs of specific safety events of interest in HF patients newly starting treatment with sacubitril/valsartan [regardless of prior use of ACEIs or ARBs])	✓	--	--	--
Primary, no 2 (IRs of specific safety events in HF patients newly starting treatment with sacubitril/valsartan [without prior exposure to ACEIs or ARBs])	--	✓	--	--
Secondary, no 1 (IRs specific safety events in HF patients newly starting treatment with ACEIs [without prior exposure to ACEIs/ARBs])	--	--	--	✓
Secondary, no 2 (IRs specific safety events in HF patients with ACEI use [(regardless of prior use of ACEIs or ARBs)])	--	--	✓	--
Exploratory, no 1 (RR assessment of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan [without prior ACEI/ARB exposure] compared to adult HF patients with ACEI exposure [without prior ACEI/ARB exposure])	--	✓	--	✓
Exploratory, no 2 (RR assessment of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan [regardless of prior ACEI/ARB exposure]) versus adult HF patients newly starting treatment with ACEIs [without prior ACEI/ARB exposure])	✓	--	✓	--

Exploratory, no 3 (RR assessment of angioedema in adult HF patients newly starting treatment with sacubitril/valsartan [regardless of prior ACEI/ ARB exposure]) versus adult HF patients with ACEI exposure [regardless of prior ACEI/ARB exposure])	✓	--	--	✓

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; HF = heart failure; RR = relative risk, IR = incidence rate

7.3.2 Safety events of interest

The safety events of interest include a recorded diagnosis of:

- Angioedema (primary event of interest; as '*narrow*' [primary analysis] and '*hypersensitivity reaction*' [sensitivity analysis])
- Hypotension (as '*narrow*' [primary analysis] and '*broad*' [sensitivity analysis])
- Hyperkalemia
- Hepatotoxicity
- Renal impairment

as identified from in- and/or outpatient registry or claims data, or electronic medical records. Recorded abnormal laboratory values (for identification of hyperkalemia) will also be included for identification of outcomes of interest, if available (not available for ARS and GePaRD).

Safety events of interest will be identified using the event-specific codes based on the coding system(s) used in the databases of interest (e.g. READ, ICD-9/-10 CM, ICD-10 GM, or ICPC codes (see Table 7-8 for details). A detailed knowledge of the healthcare systems in the different countries is necessary to provide the correct definitions for all safety events.

An initial list of terms that would be used for the event definition mapping is supplied in Annex Section 12.3. Additional natural language processing (NLP) terms will be used in PHARMO to further differentiate within ICPC codes.

7.3.2.1 Angioedema

Angioedema is characterized by non-pitting edema of the dermis and subcutaneous layers. The most common sites of involvement are the tongue, lips, face, and throat; however, swelling can also occur in the extremities, genitalia, and viscera. Life-threatening airway swelling can also occur (Lewis 2013).

For angioedema, case validation of a random sample will be performed across databases (where possible) to assess the positive predictive value (PPV) of the identification algorithms. If the PPV is below 80% we will aim to validate all cases if that is feasible and informative.

Two definitions will be used:

Narrow: angioedema events identified through disease codes [ICD-9/-10 CM, ICD-10 GM, ICPC, Read] specific for angioedema

Hypersensitivity reaction: including symptoms not necessarily specific to angioedema but indicative of potential angioedema events

Code lists and identification algorithms (e.g., with confirmatory treatments such as corticosteroids, epinephrine, or antihistamines) were created in close collaboration with the data partners and will be described in the statistical analysis plan (SAP).

For individual terms planned to identify cases with angioedema, see Annex 3 Section 12.3.1 Table 12-1.

Table 7-3 Components used to identify angioedema in the databases

	Database (country)						
	PHARMO (NL)	**HSD (IT)**	**Aarhus (DK)**	**CPRD (UK)**	**SIDIAP (ES)**	**ARS (IT)**	**GePaRD (DE)**
Codes	ICPC/ICD-10 CM	ICD-9 CM	ICD-10 CM	READ	ICD-9/-10 CM	ICD-9 CM	ICD-10 GM
Drugs	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Text* / symptoms	Yes*	Yes	No	No	No	No	No

ARS = Agenzia Regionale di Sanità della Toscana; CM = Clinical Modification; CPRD = Clinical Practice Research Datalink; DK = Denmark; DNPR = Danish National Prescription Registry; ES = Spain; GePaRD = German Pharmacoepidemiological Research Database; GM = German Modification; HSD = Health Search IMS Health Longitudinal Patient Database; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; UK = United Kingdom

*PHARMO will be the only database that will use text for natural language processing (NLP)

Note: details on databases, see Section 7.4

7.3.2.2 Hypotension

Based on the agreement of the Consensus Committee of the American Autonomic Society and the American Academy of Neurology, orthostatic hypotension has been defined as a sustained fall of ≥20 mmHg in systolic or ≥10 mmHg in diastolic blood pressure within 3 min of active standing or head-up tilt to at least 60°. In the recent revision of the consensus statement, a systolic fall of 30 mmHg was defined as orthostatic hypotension for patients with an abnormally high supine blood pressure. However, some symptomatic patients may have a much greater fall in blood pressure while standing (Robertson 2008).

Code lists and identification algorithms were created using a code-mapping program, in close collaboration with the database partners, and will be described in the SAP.

Table 7-4 provides information on the available components by database to identify events of hypotension.

Table 7-4 Components for the identification of hypotension in the databases

	Database (country)						
	PHARMO (NL)	**HSD (IT)**	**Aarhus (DK)**	**CPRD (UK)**	**SIDIAP (ES)**	**ARS (IT)**	**GePaRD (DE)**
Codes	ICPC/ICD-10 CM	ICD-9 CM	ICD-10 CM	READ	ICD-9/-10 CM	ICD-9 CM	ICD-10 GM
Text* / symptoms	Yes	No	No	No	No	No	No

ARS = Agenzia Regionale di Sanità della Toscana; CM = Clinical Modification; CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; GePaRD = German Pharmacoepidemiological Research Database; GM = German Modification; HSD = Health Search IMS Health Longitudinal Patient Database; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; UK = United Kingdom

Blood pressure will not be used to identify hypotension

Note: details on databases, see Section 7.4

*PHARMO will be the only database that will use text for natural language processing (NLP)

7.3.2.3 Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration > 5 mmol/L (Evans et al 2005). Code lists were created using a code-mapping program in close collaboration with the data partners, and will be described in the SAP.

For individual terms planned to identify cases with hyperkalemia, see Annex 3 Section 12.3.1 Table 12-1.

Table 7-5 Components used to identify hyperkalemia in the databases

	Database (country)						
	PHARMO (NL)	**HSD (IT)**	**Aarhus (DK)**	**CPRD (UK)**	**SIDIAP (ES)**	**ARS (IT)**	**GePaRD (DE)**
Codes	ICPC/ICD-10 CM	ICD-9 CM	ICD-10 CM	READ	ICD-9/-10 CM	ICD-9 CM	ICD-10 GM
Laboratory (K^+)	Yes	Yes	Yes	Yes	Yes	No	No
Text* / symptoms	Yes	No	No	No	No	No	No

ARS = Agenzia Regionale di Sanità della Toscana; CM = Clinical Modification; CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; GePaRD = German Pharmacoepidemiological Research Database; GM = German Modification; HSD = Health Search IMS Health Longitudinal Patient Database; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IT = Italy; K^+ = potassium; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; UK = United Kingdom

Note: details on databases, see Section 7.4

*PHARMO will be the only database that will use text for natural language processing (NLP)

7.3.2.4 Hepatotoxicity

Hepatotoxicity is defined as increased liver function tests [LFTs] for either ALT or AST > 3-times upper limit of normal (ULN), hepatitis: with ALT >3 x ULN and clinical symptoms of liver disease; cholestatic or mixed hepatitis with development of jaundice; acute liver failure (ALF). Laboratory values of alkaline phosphatase, ALT, or AST will not be used to identify

hepatotoxicity, because the time frames for the definition of hepatotoxicity cannot be verified, and not all databases contain laboratory values. Detailed code lists were created using a code-mapping program and will be described in the SAP.

For individual terms planned to identify cases with hepatotoxicity, see Annex 3 Section 12.3.1 Table 12-1.

Table 7-6 Components used to identify hepatotoxicity in the databases

	Database (country)						
	PHARMO (NL)	**HSD (IT)**	**Aarhus (DK)**	**CPRD (UK)**	**SIDIAP (ES)**	**ARS (IT)**	**GePaRD (DE)**
Codes	ICPC/ICD-10 CM	ICD-9 CM	ICD-10 CM	READ	ICD-9/-10 CM	ICD-9 CM	ICD-10 GM
Text* / symptoms	Yes	No	No	No	No	No	No

ARS = Agenzia Regionale di Sanità della Toscana; CM = Clinical Modification; CPRD = Clinical Practice Research Datalink; DK = Denmark; GePaRD = German Pharmacoepidemiological Research Database; GM = German Modification; HSD = Health Search CSD Longitudinal Patient Database; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

Laboratory values of alkaline phosphatase, alanine aminotransferase, or aspartate aminotransferase will not be used to identify hepatotoxicity, because the time frames for the definition of hepatotoxicity cannot be verified, and not all databases contain laboratory values.

Note: details on databases, see Section 7.4

*PHARMO will be the only database that will use text for natural language processing (NLP)

7.3.2.5 Renal impairment (acute kidney injury)

Acute renal impairment, or acute kidney injury is characterized by a rapid reduction in kidney function resulting in a failure to maintain fluid, electrolyte, and acid-base homoeostasis.

Acute kidney injury is defined when one of the following criteria is met:

- Serum creatinine rises by ≥ 26µmol/L within 48 hours or
- Serum creatinine rises ≥ 1.5-fold from the reference value, which is known or presumed to have occurred within one week or urine output is < 0.5ml/kg/hr for >6 consecutive hour

Creatinine values will not be used to identify renal impairment, because the time frames for the definition of renal impairment cannot be verified, and not all databases contain laboratory values. Code lists were created using a code-mapping program and will be described in the SAP.

For individual terms planned to identify cases with renal impairment, see Annex 3 Section 12.3.1 Table 12-1.

Table 7-7 Components for the identification of renal impairment in the databases

	Database (country)						
	PHARMO (NL)	**HSD (IT)**	**Aarhus (DK)**	**CPRD (UK)**	**SIDIAP (ES)**	**ARS (IT)**	**GePaRD (DE)**
Codes	ICPC/ICD-10 CM	ICD-9 CM	ICD-10 CM	READ	ICD-9/-10 CM	ICD-9 CM	ICD-10 GM
Text* / symptoms	Yes	No	No	No	No	No	No

ARS = Agenzia Regionale di Sanità della Toscana; CM = Clinical Modification; CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; GePaRD = German Pharmacoepidemiological Research Database; GM = German Modification; HSD = Health Search IMS Health Longitudinal Patient Database; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IT = Italy; NL = the Netherlands; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; UK = United Kingdom

Creatinine values will not be used to identify renal impairment, because the time frames for the definition of renal impairment cannot be verified, and not all databases contain laboratory values.

Note: details on databases, see Section 7.4

*PHARMO will be the only database that will use text for natural language processing (NLP)

7.3.3 Patient characteristics/demographics

The following patient characteristics at the index date will be summarized:

- Age (continuous, categorical [18-44, 45-64, 65-74, ≥ 75 years, no reference needed])
- Sex (female as reference)
- Ethnicity (only available in CPRD, but recording rather incomplete Mathur et al 2014)
- Comorbidities (i.e., diseases/conditions already prevalent before the index date, using entire available history in patients' electronic medical records (yes/no [no = reference])), i.e.
  - Hypertension
  - Myocardial infarction
  - Stroke or transient ischemic attack (TIA)
  - Angina pectoris
  - Atrial fibrillation
  - Valvular disease
  - Diabetes mellitus
  - Respiratory disease (asthma, chronic obstructive pulmonary disease [COPD])
  - Allergic reactions (e.g., to food, seasonal allergies, drug rash, urticaria)
  - Moderate to severe chronic kidney disease (CKD), will not be presented for the respective cohorts examining sacubitril/valsartan or ACEI use and the risk of renal impairment (exclusion criterion)
  - Chronic hepatic disease, will not be presented for the respective cohorts examining sacubitril/valsartan or ACEI use and the risk of hepatotoxicity (exclusion criterion)

- Comedication ((yes/no [no = reference]) to characterize patients in the respective cohorts (based on prescription/dispensing at index date or within 365 days prior to index date):
    - ACEIs (assessed excluding index date)
    - ARBs (assessed excluding index date)
    - Other renin angiotensin aldosterone system (RAAS) targeting drugs (e.g. aliskiren)
    - Beta-blockers
    - Calcium channel blockers
    - Mineralocorticoid receptor antagonists (MRAs)
    - Loop diuretics
    - Other diuretics (thiazides, potassium-sparing diuretics [excluding MRAs and loop diuretics])
    - Digoxin
    - Ivabradine
    - Nitrates
    - Hydralazine
    - Antiarrhythmic agents
    - Anticoagulants
    - Antiplatelets (including prescription aspirin)
    - Lipid lowering drugs (excluding statins)
    - Statins
    - Antidiabetics
    - Fluoroquinolones
    - Non-steroidal anti-inflammatory drugs (NSAIDs)

To approximate heart failure severity and overall health status of the patient, the use of the following will be evaluated:

- The number of cardiac drugs used in HF treatment at index date other than ACEI and sacubitril/valsartan (i.e. ARB (other than sacubitril/valsartan), direct renin inhibitors, ivabradine, beta blockers, mineralocorticoid receptor agonists (MRAs), hydralazine and isosorbide dinitrate, diuretics), counting the number of ATC codes of active compounds used in HF, dichotomized to use as a proxy for HF [≤3 (= reference), >3])

Disease and drug codes, and algorithms to identify these covariates were developed and will be described in detail in the SAP.

7.4 Data sources

This study uses European databases comprising routine health care data. This will provide a reflection of real-world circumstances and prescribing behaviors. The databases have been selected based on their geographic location, the availability of population-based data on drugs, plus their recognized reputation in the area of drug utilization, and safety research. Multiple countries are included in order to provide international data and to guarantee sufficient exposure to sacubitril/valsartan.

The data for this study will be retrieved from The Clinical Practice Research Datalink (CPRD) from the UK, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) from Spain provided by IDIAP Jordi Gol, the Health Search Database (HSD) provided by Società Italiana di Medicina Generale and the Agenzia Regionale di Sanità della Toscana' (ARS) database, both from Italy, the PHARMO Database Network from the Netherlands provided by the PHARMO Institute for Drug Outcomes Research, the Aarhus University Prescription Database and Danish National Patient Registry from Denmark provided by Aarhus University, and the German Pharmacoepidemiological Research Database (GePaRD), provided by the Leibniz Institute for Prevention Research and Epidemiology – BIPS. All data sources are listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

All analyses will be performed in collaboration between the PI – as scientific lead — and the PHARMO Institute for Drug Outcomes Research according to contractual agreements.

Table 7-8 provides an overview of database characteristics including available data. All databases have a mean follow-up ranging from 2.5 to 11 years and are representative of the country-specific populations in terms of age and gender. Databases used are primary care databases (except for the Aarhus database from Denmark, which is a prescription database) and available data are complete, as they come from the general practitioners' (GPs') electronic primary care records. The primary care databases represent 3-13% of the country specific total population. The total number of persons in the source population encompassing all seven databases will be approximately 16 million in 2016.

Table 7-8 Overview of databases used in the study

Characteristics	Database						
	PHARMO	**CPRD**	**Aarhus**	**HSD**	**ARS**	**SIDIAP**	**GePaRD**
Country (population size 2019 in million inhabitants)†	Netherlands (17.1)	United Kingdom (66.8)	Denmark (5.8)	Italy (59.2)	Italy (59.2)	Spain (46.4)	Germany (82.4)
Type of database	EMR	EMR	ADM	EMR	ADM	EMR	Claims
Number of patients, millions	4.0 (approximately 1.2 million with both GP and outpatient pharmacy data available)	5.7 (approx. 55% linked to HES data)	1.5	1.5	3.6	5.1 (about 33% linked to hospital data)	20
Date in	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of death	Yes	Yes	Yes	Yes	Yes	Yes	No
Cause of death	No	No (only available through linkage of data to the Office for National Statistics death registration data)	Yes	No	Yes	No	Yes (date of in-hospital death is available. Date of out-of-hospital death can be estimated)
Updates	Annual (October)	Yearly (May/June)	Yearly (April)	2-times a year: (30/06 and 31/12)	Every month with a lag-time of 3-4 months	Yearly (April/May)	Yearly (mid year)
Prescriptions							
Outpatient Rx	Yes	Yes (specialist incomplete)	Yes	Yes	Yes	Yes (specialist incomplete)	Yes
Coding of drugs	ATC	Gemscript codes	ATC	ATC	ATC and local Italian coding system	ATC	ATC GM

Characteristics	Database						
	PHARMO	**CPRD**	**Aarhus**	**HSD**	**ARS**	**SIDIAP**	**GePaRD**
Dosing regimen	Yes	Yes (incomplete)	No	Yes (incomplete)	No	Yes	No
Safety events of interests							
Hospitalizations	Yes	Yes (for about 55%)	Yes	Yes (if reported back by patients)	Yes	Yes (for about 33%)	Yes
Emergency visits	No	No	Yes	Yes (incomplete)	Yes	No	Yes (incomplete, only emergency visits to GPs)
Outpatient diagnoses	Yes	Yes	Yes	Yes	No	Yes	Yes (diagnoses made by GPs and diagnoses made by specialists in the outpatient setting)
Coding of disease	ICPC, ICD-10 CM	READ (ICD-10 CM for HES data)	ICD-10 CM	ICD-9 CM	ICD-9 CM	ICD-10 CM (ICD-9 CM for hospital data)	ICD-10 GM
Laboratory data	Yes	Yes	Yes	Yes	No	Yes	No (only information on date and type of test is recorded, results of tests are not available)

ADM = Administrative; ARS = Agenzia Regionale di Sanità della Toscana; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; CM = Clinical Modification; CPRD = Clinical Practice Research Datalink; EMR = Electronic Medical Records; GePaRD = German Pharmacoepidemiological Research Database; GM = German Modification; GP = general practitioner; HES = Hospital Episode Statistics; HSD = Health Search Database; ICD= International Classification of Disease, ICPC = International Classification of Primary Care; Rx = prescription; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

† derived from http://www.worldometers.info/ (accessed 13-Feb-2019)

All of the databases comply with EU guidelines on the use of medical data for medical research and have been validated for pharmacoepidemiological research (Ehrenstein et al 2010, van Herk-Sukel et al 2010, Cazzola et al 2011, Garcia-Gil et al 2011, Herrett et al 2015, Jick et al 2003, Pigeot and Ahrens 2008, Ohlmeier et al 2016, Trifirò et al 2019).

More details on the individual databases are provided in the following sections.

7.4.1 The Clinical Practice Research Datalink (CPRD) – UK

The CPRD; from the UK collates the computerized medical records of general practitioners (GPs) in the UK who act as gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals and hospitalizations. GPs act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care as necessary. Secondary care teams also feedback information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death (Herrett et al 2015). The majority of the data are coded in READ Codes (Booth 1994); however, additional text data is also available, which can improve the sensitivity and specificity of data.

Importantly, CPRD operates a careful and continual quality control procedure that ensures that only practices that are "up-to-standard" (UPS) are included in the research dataset. The dataset is generalizable to the UK population based on age, sex, socioeconomic class, and national geographic coverage.

There are currently approximately 13.2 million patients (acceptable for research purposes) – of which 5.7 million are active (still alive and registered with the GP practice) – in approximately 680 practices. Data include demographics, all GP/healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments, including all prescriptions, all data referrals to other care, hospital discharge summaries (date and Read codes), hospital clinic summary, preventive treatment and immunizations, and death (date and cause). For a proportion of the CPRD panel practices (~55%), the GPs have agreed to permit CPRD to link patient level data to hospital data, i.e. to data from the Hospital Episode Statistics (HES) database.

The HES is a data warehouse containing details of all admissions to National Health Service (NHS) hospitals in England (~168 acute care NHS Trusts) collected by the Health & Social Care Information Centre. HES is the data source for a wide range of healthcare analysis for the NHS, government and many other organizations, and individuals. The HES database contains dates of hospital admissions, primary and secondary diagnoses (coded using the ICD-10 CM classification), and related procedures (coded using the ICD-10 CM classification and Office of Population Censuses and Surveys Classification of Interventions and Procedures, Fourth Version). Linked data can be analyzed over a period from January 1997 up to the most recent available HES year (1-2 years delay).

7.4.2 Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) – Spain

GPs play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions, and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. The SIDIAP database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3,414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results.

Linked data on hospital admissions and their major outcomes are available for 30% of the practices in SIDIAP. Health professionals gather this information using ICD-10 CM codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. Recent reports have shown the SIDIAP data to be useful for epidemiological research (Garcia-Gil et al 2011).

As this is a primary care database, information on specialist prescribing, drug dispensing, and actual drug intake is missing.

7.4.3 Health Search IMS Health Longitudinal Patient Database (HSD) – Italy

The Italian arm of the study will use the Health Search IMS Health Longitudinal Patient Database (HSD), a longitudinal observational database that is representative of the Italian general population. It was established in 1998 by the Italian College of General Practitioners (Filippi et al 2005). The HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.5 million patients) located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specified training courses. The database includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses, hospital admission, and causes of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM). Drug names are coded according to the ATC classification system. To be included in the study, GPs must have provided data for at least one year and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates (Cricelli et al 2003). The HSD complies with EU, guidelines on the use of medical data for research. HSD has been used as a database for a number of peer reviewed publications on the prevalence of disease conditions, drug safety, and prescription patterns in Italian primary care (Cazzola et al 2011). Approval for use of data is obtained from the Italian College of General Practitioners.

Dose must be inferred from the strength and according to the dosing regimens of the respective Summary of Product Characteristics (SmPC) for the other drugs. Around 50% of prescribed daily dosages are also imputed by GPs.

As this is a primary care database, information on specialist prescribing, drug dispensing, and actual drug intake is missing.

7.4.4 Agenzia Regionale di Sanità della Toscana (ARS) – Italy

The Italian National Healthcare System is organized at a regional level: the regions are responsible to provide to all their inhabitants a prespecified level of assistance, with a national tax-based funding. The Tuscany Region has around 3.6 million inhabitants. The ARS database comprises all the tables that are collected by the Tuscany Region to account for the healthcare delivered to the persons that are officially resident in the region. Moreover, ARS collects tables from regional initiatives. All tables in the ARS database can be linked at the individual level.

ARS is allowed by regional law to conduct studies using its database. To conduct a study in pharmacoepidemiology, ARS requires full compliance with the ENCePP Code of Conduct.

The ARS database routinely collects primary and secondary care prescriptions of drugs for outpatient use and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from copayment, diagnostic tests and procedures, and causes of death. The lack of availability of outpatient diagnoses or laboratory data in ARS is expected to possibly shift capture of events to the more severe forms of myotoxicity and hepatotoxicity (i.e., less serious events with only increases of laboratory parameters, or the ones only requiring an outpatient visit would be missed). Acute pancreatitis is expected to ultimately result in hospitalization and is therefore not expected to be affected.

The database was established in 1999. The ARS database is updated approximately every month, with a lag time of 3-4 months. Transactional data may still be incomplete, and each year's data is consolidated by the end of March every year.

ARS and HSD do not have the same catchment area, therefore, overlap is limited (< 2%). Whereas ARS is only capturing information from the region of Tuscany, HSD is collecting information from a selected sample of GPs across the entire country (including Tuscany). However, as sacubitril/valsartan initially is mostly prescribed by specialists (cardiologists, internists, geriatricians; due to reimbursement policy), which is captured in ARS but not captured in HSD, there is a small risk of overlap between ARS and HSD. However, as sacubitril/valsartan exposure prevalence identified in HSD is very low, the risk of overlap in this study is considered negligible.

7.4.5 PHARMO Database Network – the Netherlands

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and outpatient pharmacies, clinical laboratories, hospitals, cancer, pathology and perinatal registries,

are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the used record linkage methods can be found elsewhere (van Herk-Sukel et al 2010).

The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. However, the data collection period, catchment area, and overlap between data sources differ. Therefore, the final cohort size will depend on the data sources included. As data sources are linked on an annual basis, the average lag time in data availability is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status, and mortality. Other available information depends on the data source used. To address the objectives of the present study the following PHARMO databases will be used: General Practitioner Database, Out-patient Pharmacy Database and Hospitalisation Database.

GP Database comprise data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity, and route of administration. Drug prescriptions are coded according to the ATC Classification System. Diagnoses and symptoms are coded according to the ICPC, which can be mapped to ICD codes, but can also be entered as free text.

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by outpatient pharmacies. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drug dispensing are coded according to the ATC Classification System.

The Hospitalisation Database comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required from the national Dutch Hospital Data Foundation. The records include information on hospital admission and discharge dates, discharge diagnoses and procedures. Diagnoses are coded according to the ICD codes and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures which links to the Dutch Healthcare Authority (NZa) declaration codes and the Dutch Classification of Procedures.

Combined GP, out-patient pharmacy and hospitalisation data currently cover a catchment area representing 1.2 million residents.

7.4.6 Aarhus University Prescription Database – Denmark

The Aarhus University Prescription Database comprises clinical and prescription data on the population of former North-Jutland, Aarhus, Rinkjebing and Viborg counties, which since 2007 are called the Central Denmark Region and the North Denmark Region. This population covers a total of 1.8 million inhabitants and is representative of the population of Denmark (Ehrenstein et al 2010). Data available on these subjects comprise their eligibility, dispensing data,

hospitalizations and procedures. Moreover, the population can also be linked to other National Danish registries. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information about the name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data can be linked to the national registry of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics. Diagnosis codes and procedures are registered. These databases have been used in numerous studies and are proven valid for pharmacoepidemiological research (Sørensen and Larsen 1994).

Dose must be inferred from the strength, and according the dosing regimens of the respective SmPC of the other drugs. The main drawbacks of the Aarhus University Prescription Database are a lack of nationwide coverage and the absence of data of certain medication types (non-reimbursed drugs, OTC drugs or drugs dispensed directly to hospital patients or outpatient clinics).

7.4.7 German Pharmacoepidemiological Research Database (GePaRD) – Germany

Since 2004, the Leibniz Institute for Prevention Research and Epidemiology – BIPS has been working on the establishment and maintenance of GePaRD. GePaRD is based on claims data from statutory health insurance (SHI) providers, and currently includes information on about 25 million persons who have been insured with one of the participating providers since 2004. Per data year, there is information on approximately 20% of the general population from all geographical regions of Germany.

In addition to demographic data, GePaRD contains information on drug dispensing, outpatient and inpatient services, and diagnoses starting with the year 2004. New data are added on an annual basis. Before data are entered into the GePaRD database they are pseudonymized and validated through numerous plausibility checks. The entire process from data delivery to availability for studies can take up to two years, e.g., data from the year 2015 cannot be used before 2017.

GePaRD is linked via the central pharmaceutical number to information from a central pharmaceutical reference database established at Leibniz Institute for Prevention Research and Epidemiology – BIPS (Leibniz Institute for Prevention Research and Epidemiology – BIPS 2017). GePaRD is compliant with EU guidelines on the use of medical data for medical research and has been validated for pharmacoepidemiological research (e.g. Pigeot and Ahrens 2008, Ohlmeier et al 2016).

7.5 Study size/power calculation

Since the primary objective of the study is to estimate the IR of angioedema and other safety events of interest with sacubitril/valsartan, Figure 7-3 presents CIs expected for angioedema, the rarest of all the events, given different sample sizes. An IR of angioedema following sacubitril/valsartan was set to be 5.5/1,000 PYs, based on an IR of 2.9/1,000 PYs following

ACEI estimated via meta-analysis, using data up to 1 year from three observational retrospective cohort studies (Figure 7-5 and Table 7-9, random effect Poisson model using data from Burkhart et al 1996, Miller et al 2008, and Toh et al 2012) and set to an IR ratio sacubitril/valsartan/ACEI of 1.9, based on the results of the double-blind part of the pivotal phase III study PARADIGM (McMurray et al 2014). Figure 7-4 shows expected CIs for the hazard ratio (HR) of sacubitril/valsartan versus ACEI for angioedema (exploratory objective [see Section 6.3]) for different sample sizes. In addition to previous assumptions on sacubitril/valsartan and ACEI IRs, the same exposure for sacubitril/valsartan and ACEIs was added.

With these assumptions, it is aimed to approximately have 24,000 PY of exposure with sacubitril/valsartan, which will provide an estimated IR of 5.5/1000 PY [95% CI: 4.6-6.5], if we observe 132 angioedema cases.

Figure 7-3 Examples of confidence intervals for the incidence rate of angioedema after exposure to sacubitril/valsartan

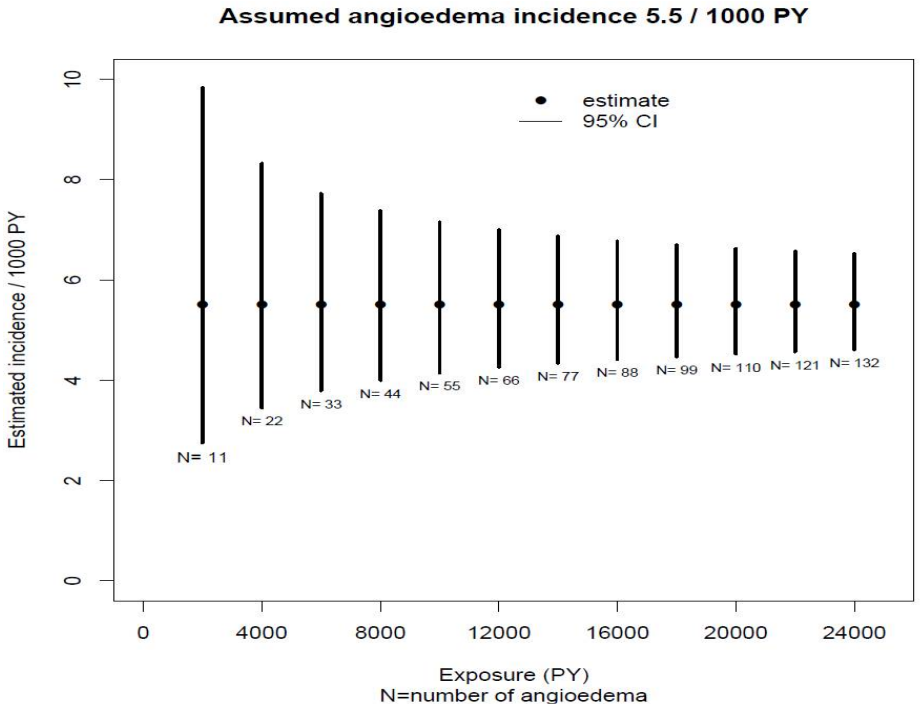


Figure 7-4 Examples of confidence intervals for the hazard ratio (HR) of angioedema after exposure to sacubitril/valsartan versus ACEI

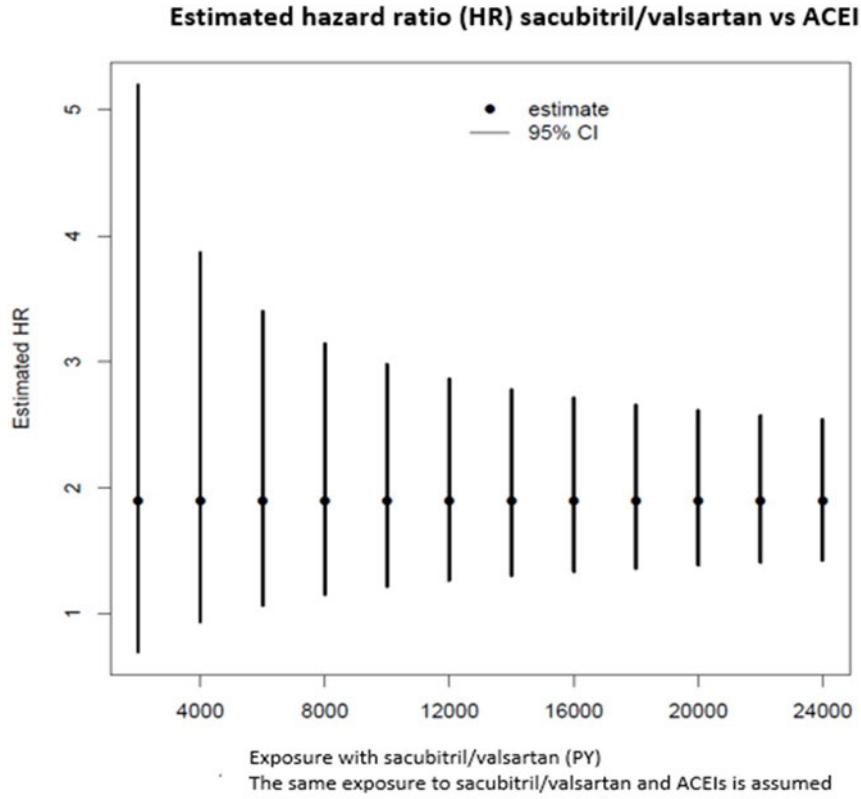


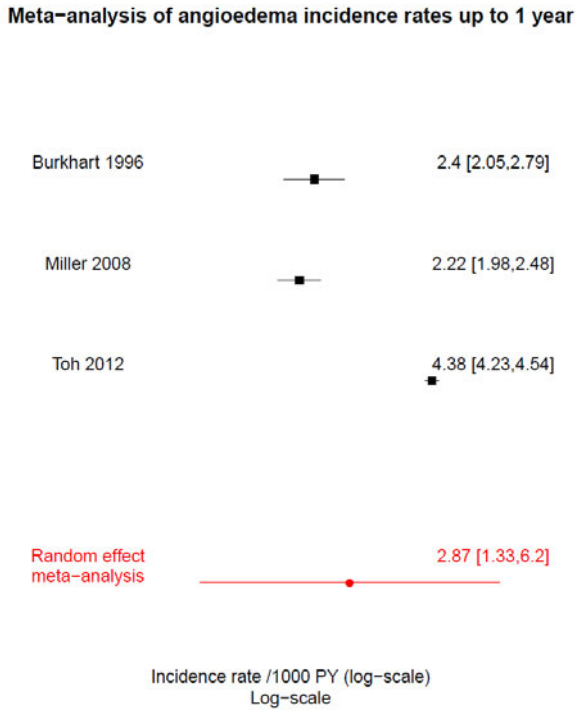
Table 7-9 Literature information for the meta-analysis of angioedema incidence rate following ACEIs

Reference	Database	Years	HF (%)	Number of Angioedema cases up to 1 year	Patients	Exposure Up to 1 year (PYs)	IR (per 1000 PYs)	95% LCL	95% UCL
Toh et al (2012)	Mini-sentinel	2001-2010	2.2	3301	1,845,138	753,105	4.38	4.24	4.54
Miller et al (2008)	VA	1999-2000	20.3	319*	195,192	143,623	2.22*	1.98*	2.48*
Burkhart et al (1996)	Medicaid	1986-1992	NA	168*	155,258	69,966	2.40*	2.05*	2.79*

ACEI = angiotensin converting enzyme inhibitor; IR = incidence rate; LCL = lower confidence limit; PY = patient-year; UCL = upper confidence limit; VA = Veterans Affairs; NA= not available; .HF= patients with HF diagnosis

*Calculated from the published data

Figure 7-5 Meta-analysis of angioedema incidence rates up to 1 year after exposure to ACEI



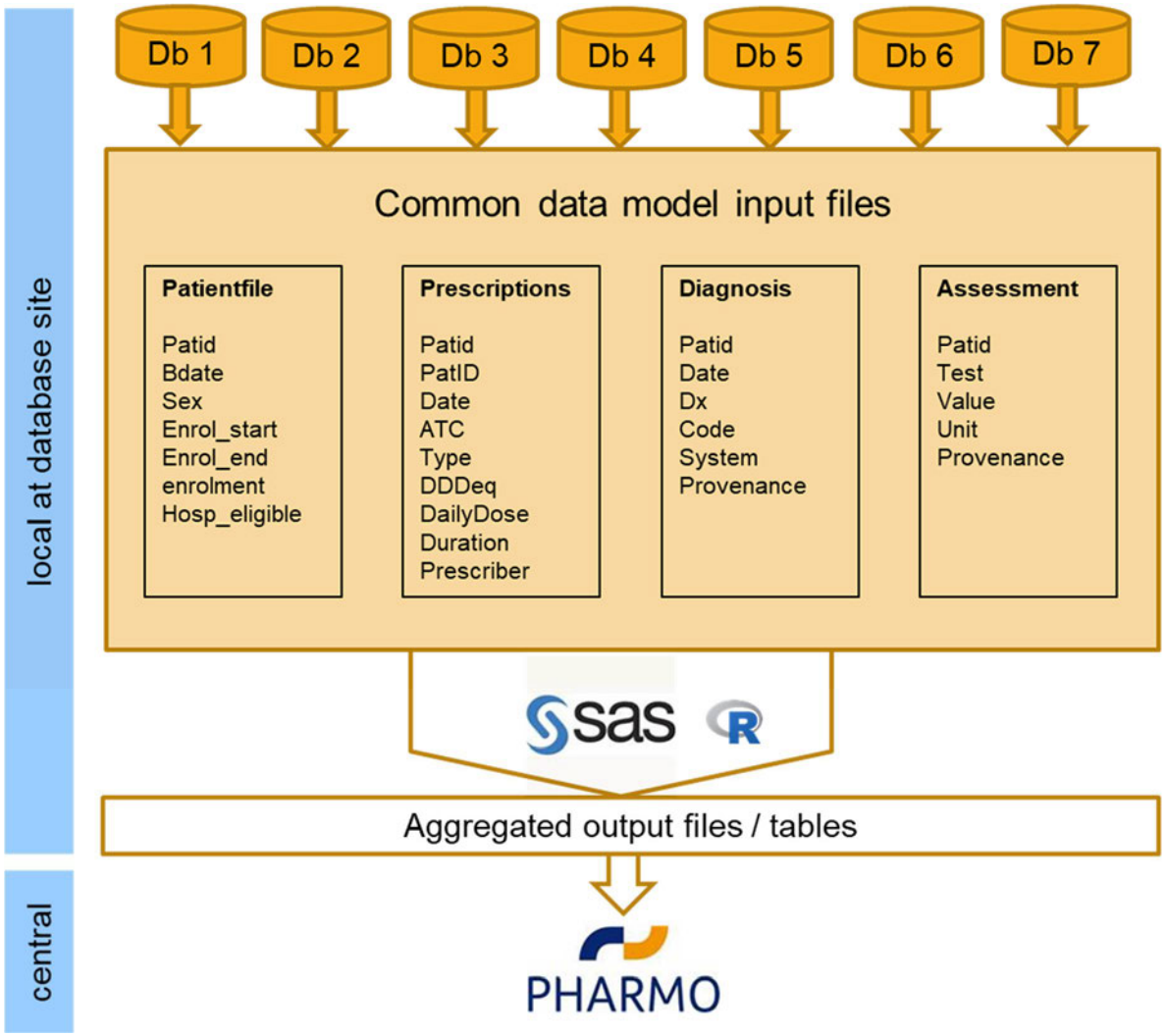
Source data from: Burkhart et al (1996), Miller et al (2008), Toh et al (2012)

7.6 Data management

7.6.1 Data collection and processing

Data collection and processing will be done locally according to a common data model. while pooling of aggregated data in a meta-analysis will be done at PHARMO (see Figure 7-6 for overview).

Figure 7-6 Model for data sharing and processing



A distributed common data model approach will be used to analyze data in an efficient manner. Each database extracts study specific data locally and transforms them into a simple common data model that has the same structure across all sites, i.e., standardized patient, medication, diagnosis, and assessment files, linkable via a patient unique identifier (see Figure 7-5), as defined in a data dictionary. Based on the relevant diagnostic codes and key words (for free text search in the PHARMO GP Database only), a data processing algorithm will be constructed for each safety event based on the consensus of the data partners, and lead to potential safety events

in the input files. The required variables have been defined by the coordinating center and are captured in a data dictionary with instructions, which is sent to the participating partners. To verify extractions and transformations, a quality check script is sent to the data partners. The output is shared with the coordinating center and compared to other sites, and subsequently discussed with the sites, who then can update the data if errors are detected. This process is repeated until quality is sufficient.

Validation of the safety event angioedema and algorithms is ongoing, and is planned to be finalized end of Q1 2022, i.e. before the final LCZ696B2014 study report (due Q4 2022).

7.6.2 Programming

All programming for local data transformation of the input files into relevant evidence for the study objectives is created in SAS by PHARMO. At Aarhus, HSD, PHARMO, SIDIAP, CPRD, and GePaRD SAS version 9.4 or higher (SAS Institute Inc., Cary, North Carolina) are used for data extraction and transformation. At ARS, R (R Foundation for Statistical Computing, Vienna, Austria) is used for data transformation (since ARS does not have a SAS license). ARS will create the data transformation program in R, based on the SAS script that is supplied by PHARMO. Using a simulated dataset, the comparability of the SAS and R programs is verified. The SAS or R programs will be run locally by the data partners against the common data model to generate the analytical datasets on individual level.

Due to the different database characteristics and coding schemes it is not possible to use one single data extraction algorithm for all of the databases. To reconcile differences across terminologies, a shared semantic foundation will be built for the definitions of safety events by selecting diagnostic codes, matching the mapping terms listed in Table 12-1, and seting up a multi-step and iterative process for the harmonization of safety event data (Trifiro et al 2014). The sequential steps of this process are shortly described below:

All safety events, risk factors, or potential confounders, will be ascertained using a list of agreed ICD-9/-10 CM (Denmark, Italy, the Netherlands, and Spain), ICD-10 GM (Germany), ICPC (the Netherlands), WCIA (the Netherlands), and READ (UK) codes. The proposed lists of codes will be created following a number of steps:

- Case definition of the safety events of interest (e.g. angioedema)
- Preliminary list of concept identifiers by searching web-based lists of ICD-9/-10 CM, ICD-10 GM, ICPC, and WCIA codes and descriptions, and mapping READ codes to the ICD codes;
- Addition of codes found after literature review of validated lists of codes for each of the safety event of interest in each of the databases;
- In addition, for the PHARMO GP Database, where free text is available and ICPC coding is not mandatory and often insufficiently granular to find specific diagnoses, the labels of the codes are considered for free text search of the safety events.
- Consensus with partners involved in the management and analysis of each of the databases, thereby data sources. As coding might change over time, relevant codes might be updated during the course of the project. Harmonization and operationalization of these

code lists will take place between databases by comparison of population-based age and sex standardized IRs, according to standard quality assurance procedures (see below).

Definition of data extraction algorithm

Based on the relevant diagnostic codes and key words (for free text search), a data extraction algorithm will be constructed for each safety event based on the consensus of the data partners. This data extraction algorithm will then be implemented by all data partners.

Event data extraction

Subsequently, each data partner extracts data locally and transforms them into a simple common data model, i.e. standardized patient, drug, and event files linkable via a patient unique identifier.

Benchmarking of incidence rates of events

For each safety event of interest and covariate we benchmark database specific IRs and frequencies for the covariates, using SAS and R scripts in a quality run. The observed IRs are compared to IRs estimated from previous database studies and literature. Outliers are identified and further investigated in an iterative manner.

This multi-step process was used successfully in several other European multi-database projects (Trifiro et al 2014). It maximizes the involvement of data partners in the study by utilizing their knowledge on the characteristics and the process underlying the data collection. After completion of harmonization, output tables for calculation, and analysis of safety events of interest will be created by the local data processors.

The difference in incidence of angioedema using only data from GP systems and the incidence of angioedema obtained from also secondary care data will be investigated.

Data elaboration

A standardized SAS script and instructions will be created by the PHARMO Institute for Drug Outcomes Research, using SAS (version 9.4). ARS will recreate the scripts in R and outcome tables will be compared.

7.6.3 Missing data

Since the underlying data represent attended medical care, we generally assume that absence of information of clinical events means absence of that condition. Life-style data, e.g. BMI and smoking, are in particular opportunistically recorded. If data on such factors are missing, this occurs generally ‘not at random’ but lack of data may indicate that recording of these factors is of no direct clinical importance. For that reason, no imputation will be done for missing data. Instead, missing data will be summarized in a separate category and the missing-indicator method will be used. Lack of information on risk factors such as smoking, or the use of certain drugs may occur, but this is unlikely differential. Information on race is only available in CPRD. Since this information is lacking in a large proportion of the data and the proportion of black patients (relevant to the safety event of angioedema) is available in <0.5% of patients, race will be reported descriptively and will not impact the analyses.

7.6.4 Data sharing

If necessary, aggregated data output from SAS scripts will be shared by data partners with the PHARMO Institute for further analyses and pooling.

The results are sent to PHARMO, using a secure file transfer protocol.

7.7 Data analysis

All analyses will be performed in collaboration between the PI, as the scientific lead, and the PHARMO Institute for Drug Outcomes Research, the coordinating center for this multi-database study. Data will be deposited in the Remote Research Environment and participating data partners can inspect the analysis by remotely accessing.

For Aarhus, HSD, SIDIAP, CPRD, and GePaRD SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) is available for data processing and analysis. At ARS, R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) will be used for data processing and analyses. SAS programs will be used by data partners to generate aggregated data files to create interim reports. Since ARS does not have a SAS license, the ARS database used SAS programs shared by PHARMO to create transformation programs in R. These R programs will be compared with SAS programs by looking at the results using simulated data.

Linkage to hospital data (CPRD, SIDIAP, PHARMO) is used where feasible to supplement the basic datasets that include regular data available from the databases. In these databases, the study objectives will be assessed in the full population (with or without linkage), and – as a stratified analysis – in a subgroup of patients with linked hospital data (linked data is currently available for approximately 55% of the full CPRD population, about 33% of the population in SIDIAP, and about 75% of the population in PHARMO).

A detailed description of the analyses is provided in the SAP and has been updated along this protocol amendment.

7.7.1 Analyses timing

7.7.1.1 Yearly analysis for interim reports

Interim reports will be submitted on a yearly basis with a first report using data until 31 Dec 2016. Data will be available in all databases with a delay of up to 12 months, i.e. Q2 2017 for data up to 31 Dec 2016 and 9 months in PHARMO (i.e. data up to 31 Dec in a given year available in Q3 of the following year). GePaRD has a data lag time of up to 2 years. The first interim report was submitted in Q1 2018. The last interim report is due in Q1 2022.

These interim reports will include the following information:

- Number of patients in the different exposure cohorts
- Patient exposure in the different exposure cohorts
- Baseline characteristics in terms of demographics, comorbidity, and concomitant medication use at the index date of the different exposure cohorts
- IRs with 95% CIs for the safety events of interest by week of use

Since validation takes time, validated IRs (for the primary safety event angioedema) will be made available for the final analysis.

7.7.1.2 Final analysis

The final analyses will be conducted at the end of the study with cumulative study data available at the time of data extraction around December 2021. The expected study period by database is presented earlier in Table 7-1.

7.7.1.2.1 Demographic and baseline characteristics of exposure cohorts

Demographic and baseline clinical characteristics of adult patients with HF initiating sacubitril/valsartan or ACEIs will be described, using contingency tables for categorical variables and mean, standard deviation (SD), range, median and interquartile range (IQR) for continuous variables in each database. Differences in demographic and baseline characteristics of adult patients with HF initiating either sacubitril/valsartan or using an ACEI will be assessed via standardized mean differences (SMD). A cross tabulation of age groups and sex will be provided for adult patients with HF initiating either sacubitril/valsartan or using an ACEI.

Information on cohort attrition will be provided in a study diagram and table. Treatment-related information (e.g. treatment duration, reason for discontinuation, switch/add-on therapy, etc.) will be summarized per treatment cohort.

In this context, we also aim at investigating the 36-hour washout period recommended in the SmPC of sacubitril/valsartan for patients previously using ACEI who started on sacubitril/valsartan in actual clinical care setting as requested by the PRAC. The current proposal is to assess the proportion of adult patients with HF initiating sacubitril/valsartan for whom there is evidence indicating concurrent use during the 36-hour period. This will be performed by assessing the proportion of sacubitril/valsartan users with concurrent prescriptions (or pharmacy fills) of ACEI (i.e. on the same day). Concurrent prescriptions (or pharmacy fills) are the only reliable indicator of non-adherence to the 36-hour washout period (see also Section 7.10).

7.7.1.2.2 Analyses of primary, secondary and exploratory objectives

For databases with a partial linkage to hospitalization data, the linked and unlinked subsets will be analyzed separately, to allow interpretation of additional hospital diagnoses in the analyses. This will be applied across all data analyses.

The COVID-19 pandemic has caused disruption of the health care systems from 2020 onward. In order to assess its impact on the analyses, the primary analysis will focus on the pre-COVID period, which is censored at 31 December 2019. The primary and secondary objectives (the period until the latest extraction date) will be assessed in the full study period as a sensitivity analysis.

Primary objective analysis

We will separately estimate the risk of the safety events of interest (i.e. angioedema [primary endpoint; '*narrow*' and hypersensitivity reactions as part of '*hypersensitivity reactions*' definition], hypotension [using both a '*narrow*' and a '*broad*' definition], hyperkalemia,

hepatotoxicity, renal impairment) as IRs, i.e. as the number of safety events of interest divided by person-time, along with 95% CIs in cohorts 1-2 (per database and pooled, using a meta-analytical approach [details will be provided in the SAP]):

1. Cohort 1: HF patients newly starting treatment with sacubitril/valsartan (regardless of prior use of ACEIs or ARBs)
2. Cohort 2: in the sub-population of HF patients newly starting treatment with sacubitril/valsartan without prior exposure to ACEIs or ARBs.

In addition, we will estimate IRs and cumulative incidence for angioedema at pre-defined time points (e.g. at Week 1, Week 4, Week 8, Week 26, and Week 52 after the index date) during use.

Secondary objective analysis

We will estimate IRs with 95% CIs (for all safety events of interest) and cumulative incidences (for angioedema only) in cohort 3 and 4 (by database and pooled, using a meta-analytical approach (details will be provided in the SAP).

In addition, we will estimate IRs and cumulative incidences for angioedema at pre-defined time points (e.g. at Week 1, Week 4, Week 8, Week 26, and Week 52 after the index date) during use (equal to the primary analysis, above).

In a subset of patients from cohort 3 (mix of prevalent and incident ACEI users at index date), we will conduct a sensitivity analysis to calculate the IR considering various different prevalent ACEI exposure periods prior to the index date.

Exploratory objective analyses

Adjusted relative risks for the primary safety event of interest (angioedema ['*narrow*' definition]) will be estimated for each database as HRs with 95% CIs using Cox regression models comparing:

a. new users of sacubitril/valsartan who are treatment-naïve to ACEIs and ARBs (cohort 2) to new users of ACEIs who are treatment-naïve to ACEIs/ARBs (cohort 4)
b. new users of sacubitril/valsartan regardless of prior ACEI/ARB use (cohort 1) to users of ACEIs who are treatment-naïve to ACEI/ARB use (cohort 4)
c. new users of sacubitril/valsartan regardless of prior ACEI/ARB use (cohort 1) to users of ACEIs regardless of prior use of ACEIs/ARBs (cohort 3)

Comparative analyses will be conducted separately in each database; pooled estimates will be provided by using a meta-analytical approach (details to be provided in SAP).

Confounding

To display differences in the cohorts we will create a propensity score (PS) of (pre-defined) co-variates for cohort 2 versus cohort 4; cohort 1 versus cohort 3; and cohort 1 versus cohort 4.

For the exploratory analyses we will adjust for the PS to limit confounding or potential channeling by applying PSOW (propensity score overlap weighting) (Li et al. 2018, Li et al. 2019, Mao et al. 2018), as a confounder control in multivariable regression models will be limited by the relatively low number of safety events and matching on PS would likely cause

loss of sacubitril/valsartan users that cannot be matched in case overlap of propensity scores is limited. Details will be provided in the SAP.

7.7.1.2.3 Sensitivity analyses

Details on sensitivity analyses will be specified in the SAP, including potential safety event misclassification, potential COVID-19 impact, and the impact of duration of prevalent ACEI use in a subset of cohort 3. In the (ongoing) validation study, the proportion of true angioedema cases among the hypersensitivity reactions is calculated as the false negative rate (FNR). The FNR will be used to estimate what proportion of angioedema events might have been missed with the narrow definition of angioedema.

7.8 Quality control

Standard operating procedures at each research center will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

At PHARMO all SAS programs will be reviewed independently by a senior researcher with a statistical and programming background. The statistical analysis plan and study reports will undergo quality control and senior scientific review.

The recreation of shared SAS programs in R by ARS will provide additional quality control of the programming codes. Double programming in SAS and R also allows checking the actual analyses to see if both programs provide the same outcomes with the same data.

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2011). All data partners have experience in conducting pharmacoepidemiologic research, and research is done by researchers trained in pharmacoepidemiology. All databases are representative of the respective countries, and database specific disease prevalence rates are in line with what has been published before.

All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Validated software (SAS version 9.4, SAS Institute Inc., Cary, NC) will be used for statistical analyses.

7.9 Limitations of the research methods

The most important uncertainty is the use of sacubitril/valsartan, which may decrease the precision of the estimates from the study. We expect major issues with the number and selection of the sacubitril/valsartan and ACEI cohorts that are naïve to prior ACEI/ARB exposure. Difference between cohorts will be inspected by covariates (baseline characteristics) and a propensity score.

The limitations of this study will be mainly due to the availability and level of detail of data. Not all potential confounders (e.g. life style factors such as smoking, BMI) are contained in the databases, and not all variables contain the information in desired detail. We will be missing

information on race – which is an important risk factor and effect modifier for angioedema – in most databases. However, we will use available information on race (e.g. from CPRD) in a sensitivity analysis. Particularly, information on the prescribed dose and duration of a prescription is not contained in all databases and has to be estimated, which might lead to misclassification of exposure. None of the databases have data on actual drug intake. This implies that we do not know whether the patient actually took the drug. Assessment of the 36-hour washout period is therefore limited to determining concurrent prescriptions (or pharmacy fills) of ACEI and sacubitril/valsartan on the same day. As angioedema risk is higher if sacubitril/valsartan is started before the determined washout period from ACEI, the risk of angioedema in cohort 1 may be slightly overestimated.

Sacubitril/valsartan treatment is likely to be initiated by specialists. CPRD and HSD have information on prescriptions from primary care only, but the other databases have data on dispensed drugs from both primary care and specialist outpatient care. Inpatient drug use is not available in any databases. This means that initiation of sacubitril/valsartan prescription (or pharmacy fill) may be missed if that took place in a setting not captured by the databases. Given that angioedema is more likely to occur shortly after treatment initiation, exposure misclassification may bias the results. Each of the databases carefully assessed how this type of bias can be mitigated, i.e. by verifying prescription (or pharmacy fill) durations, or examining referrals to specialists in the 3 months prior in the feasibility study (section 7.1.2) [redacted]. The time between referral or hospitalization for HF and first identified sacubitril/valsartan prescription (or pharmacy fill) in CPRD, HSD, GePaRD, and PHARMO was between 0 and 20 days for most sacubitril/valsartan users. In SIDIAP, this was more than 30 days for most patients. It seems plausible that for a number of these patients the first sacubitril/valsartan prescription may have been missed, either because inpatient prescribing is not present in all databases or outpatient specialist prescriptions are not captured (CPRD, HSD). The impact of misclassification of treatment start cannot be assessed with sensitivity analyses, because patients with an angioedema event during treatment that is not captured, will not have subsequent out-patient prescription records for sacubitril/valsartan that are captured, and therefore will not be included in the sacubitril/valsartan cohorts. If initiation of sacubitril/valsartan use is missed, but later exposure is captured, exposure time will be slightly underestimated and safety event rates may be slightly overestimated.

There is a risk that prescribing sacubitril/valsartan may be channeled to patients with more severe HF, especially in the UK, where The National Institute for Health and Care Excellence (NICE) has issued a draft guidance recommending sacubitril/valsartan for treatment of chronic HfrEF in NYHA Class II-III symptom patients who take a stable dose of ACEIs and who have a left ventricular ejection fraction of 35% or less (National Institute for Health and Care Excellence 2015). To fully control for HF severity may be difficult as information on NYHA class or ejection fraction was not or only partially available across all databases and proxy measures for HF severity may not fully address this kind of channeling bias. This bias may specifically affect the comparative analyses for the relative risk assessment of angioedema (exploratory objectives, see Section 6.3). In addition, any choice of ACEIs (either prevalent or incident use) as comparator group, may be associated with some sort of bias. As indicated in the SmPC, sacubitril/valsartan is contraindicated in patients with a history of angioedema related to previous ACEI or ARB treatment or with hereditary or idiopathic angioedema. Thus,

patients initiating sacubitril/valsartan will likely have a low baseline risk of angioedema (since patients who experienced an angioedema event while on ACEI/ARB treatment should not be part of the sacubitril/valsartan patient pool). ACEI initiators who are treatment naïve to ACEIs/ARBs will, however, have a higher baseline risk of angioedema since this population includes all patients who are susceptible to an angioedema event. Thus, comparing sacubitril/valsartan initiators regardless of their prior exposure to ACEIs/ARBs to ACEI initiators who are ACEI/ARB treatment-naïve could bias the comparative analysis in favor of sacubitril/valsartan. However, the comparison of sacubitril/valsartan initiators who are treatment-naïve to ACEIs/ARBs versus ACEI/ARB treatment-naïve ACEI initiators which we consider the most accurate comparison, may be underpowered due to the small sample size of treatment-naïve sacubitril/valsartan initiators. The size of the cohort of ACEI/ARB treatment-naïve ACEI initiators was sufficiently large for any analyses, which is the reason why we considered the inclusion of a historical group of ACEI/ARB treatment-naïve ACEI initiators to be unnecessary.

A comparison of sacubitril/valsartan users with prevalent ACEI users would likely bias against sacubitril/valsartan. In the group of prevalent ACEI users, the risk of angioedema can be expected to be relatively low, as patients with prior ACEI-associated angioedema should not be included, and patients with long term ACEI exposure have a lower risk as compared to new ACEI users (see also Section 7.1.1).

Misclassification of endpoints (safety events), as well as confounders is possible. For the different databases that will be used, validation studies have shown that coding is reliable in the databases and that these databases are suitable for pharmacoepidemiologic research. For those databases where free text is available (PHARMO, HSD, CPRD, and SIDIAP), validation of the safety events of interest will be conducted. Comparison of IRs of safety events of interest among databases in the quality run will allow checking for internal and external validity. The validation study will also assess validity in the other databases based on a patient profile review of available information.

For all databases, apart from Aarhus, it should be noted that the primary aim of data collection is patient management or reimbursement, and not medical research. This implies that only events are collected which are deemed to be relevant for patient care. In addition, information from specialists is incomplete in majority of the databases. The databases that capture all prescriptions or pharmacy fills (primary and secondary care) are Aarhus, PHARMO, ARS, and GePaRD. The other databases are primary care databases and do not capture (all) prescriptions from medical specialists. However, in all of these countries (UK, Italy, and Spain), prescriptions initiated by the specialist are generally continued by the GP.

Finally, there are differences in timing of data updates in the various databases (medical records are continuously updated, administrative databases are updated once per year in most instances). However, as data extraction will be repeated during the course of the study, this should allow for the most recent and “up-to-date” data to be used.

7.10 Other aspects

At the explicit request of the PRAC, Novartis committed to investigate the 36-hour washout period recommended in the SmPC of sacubitril/valsartan for patients previously using ACEI

and who started on sacubitril/valsartan in actual clinical care setting. This washout period should lower the potential risk of angioedema when a patient is exposed to both sorts of medicines at one time. Given the nature and limitations of database research, however, such a research question is difficult to operationalize. The MAH, Primary Investigator and Database Custodians have assessed how to optimally implement this research question and will report the concurrent prescriptions (i.e. on the same day) of ACEI and sacubitril/valsartan as violation of the recommended washout period.

8 Protection of human subjects

For this study, participants from various EU member states will process personal data from individuals collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects, and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All of the databases used in this study are currently used for pharmacoepidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. According to these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which will generate nonidentifiable data with less detailed information that will be pooled across databases.

The output files are shared with PHARMO, who will incorporate them into the reports, or combine them for pooled analyses. These output files do not contain any data that allow identification of subjects included in the study. In fact, each record is completely anonymous and does not contain any identifier key.

The protocols will be reviewed by the Institutional Review Boards (IRBs) of the respective databases. As this is a non-interventional study, there is no need for ethical approval in the Netherlands, Germany, UK, Denmark, and Italy. For Germany, studies that are based on GePaRD are exempt from IRB according to the Ethics Committee of the University of Bremen. For SIDIAP (Spain), both the scientific committee for SIDIAP studies and the local ethics committee will evaluate the protocol before the study can be carried out.

Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a ‘European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study’ and follows the ‘ENCePP Code of Conduct’ (European Medicines Agency 2011).

9 Management and reporting of adverse events/adverse reactions

As this is a non-interventional study based on secondary use of data (from various EU electronic healthcare databases), safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and a safety event of interest. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

For applicable non-interventional PASS (in the EU or mandated by an EU Health Authority outside the EU), the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

Not applicable.

12.2 Annex 2 – ENCePP checklist for study protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

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

Study reference number:

LCZ696B2014

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16-20
2.1.2 The objective(s) of the study?	☒	☐	☐	20, 21
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	25, 26
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☒	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	21
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	31
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	52,53

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	25, 26
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	26

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.2 Age and sex?	☒	☐	☐	26
4.2.3 Country of origin?	☒	☐	☐	26
4.2.4 Disease/indication?	☒	☐	☐	26
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	25, 26, 27

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	28-29
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	28
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	29
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	31-35
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity,	☒	☐	☐	31-35

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)				

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	53, 54
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	55

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	36-44
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	36-44
8.1.3 Covariates?	☒	☐	☐	36-44
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	36-44
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	36-44
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	36-44
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	11, 38-39

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	11, 38-39
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	11, 38-39
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	48

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	44-45

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☐	☐	☒	
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	50

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	54
11.3 Are methods of quality assurance described?	☒	☐	☐	54
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☐	48-49
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	44
12.1.2 Information biases?				
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	54-55
12.3 Does the protocol address other limitations?	☒	☐	☐	54-56

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	57-58
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	57

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	13-14

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	58
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	58

Comments:

Name of the main author of the protocol: [redacted]

Date: / /

Signature: _____

12.3 Annex 3 – Additional information

12.3.1 Terms to be used for mapping of outcomes

Table 12-1 Terms to be used to identify cases with the outcomes of interest

Outcome of interest	Terms to be used	Comments
Angioedema	ICD-9/-10CM/ICD-10GM/Read/ICPC codes corresponding to angioedema, angioneurotic edema, Quincke edema, or any other synonym	Primary analysis ('*narrow*' definition)
	Allergic oedema, Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Angioedema, Bronchial oedema, Circumoral oedema, Endotracheal intubation, Epiglottic oedema, Gastrointestinal oedema, Genital swelling, Gleich's syndrome, Intestinal angioedema, Laryngeal dyspnoea, Laryngeal obstruction, Laryngospasm, Laryngotracheal oedema, Genital oedema, Mouth oedema, Oropharyngeal spasm, Palatal oedema, Penile oedema, Penile oedema, Periorbital oedema, Pharyngeal oedema, Reversible airway obstruction, Scrotal oedema, Scrotal swelling, Skin oedema, Swelling face, Swollen tongue, Tongue oedema, Tracheal obstruction, Tracheal oedema, Upper airway obstruction, Vaginal oedema, Visceral oedema, Vulval oedema, Vulvovaginal swelling	Sensitivity analysis including additional terms on top of the above ('*broad*' definition) Specifically excluded [because too unspecific, risk of too many false positives]: Endotrachael intubation, Reversible airway obstruction, Skin oedema, Upper airway obstruction 'Endotrachael intubation' to be used however, in the context of assessing severity of angioedema (if available/feasible)
Hypotension	Hypotension, Blood pressure decreased, Orthostatic hypotension, Dizziness, Postural dizziness, Presyncope, Syncope	Specifically excluded [because too unspecific, risk of too many false positives]: Depressed level of consciousness, Loss of consciousness No BP measurements to be included to identify cases of hypotension Sensitivity analysis for syncope (as a proxy for severe hypotension)
Hyperkalemia	Hyperkalemia, Blood potassium increased	Include lab values for potassium measurements; definition: K^+ >5.4 nmol/l
Hepatotoxicity	Acute hepatic failure, Drug-induced liver injury, Hepatic failure, Hepatic necrosis, Acute hepatitis, Fulminant hepatitis, Toxic hepatitis, Hepatocellular injury, Hepatorenal failure, Hepatotoxicity, Liver injury, Hepatic encephalopathy	--

Renal impairment	Acute kidney injury, Acute nephropathy, Acute prerenal failure, Anuria, Azotaemia, Dialysis, Toxic nephropathy, Renal failure, Renal impairment	--