NOVARTIS

Quantitative Safety and Epidemiology

Non-Interventional Study Protocol

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	v00
Date of last version of protocol	24 November 2016
EU PAS register number	Not registered
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	With this non-interventional study, real-world data will be

and objectives	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, Italy, the Netherlands, Spain, United Kingdom
Author	[redacted]

[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited Frimley Business Park Camberley GU16 7SR United Kingdom
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Table of contents

List of figures

List of tables

List of abbreviations

ACE(I)	Angiotensin Converting Enzyme (Inhibitor)
ADM	Administrative
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CRO	Contract Research Organization
Db	Database
DK	Denmark
EMA	European Medicines Agency
[redacted]	[redacted]
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ES	Spain
EU	European Union
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
HES	Hospital Episode Statistics
HF	Heart Failure
HF-rEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
HSD	Health Search IMS Health Longitudinal Patient Database (HSD)
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
MRA	Mineralocorticoid Receptor Antagonist
MC	Medical Center
NEP	Neutral Endopeptidase
NHS	National Health Service
NIS	Non-Interventional Study
NL	The Netherlands
NYHA	New York Heart Classification
OTC	Over-the-Counter

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
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
PY	Patient-Year
RAAS	Renin-Angiotensin-Aldosterone System
RMP	Risk Management Plan
RRE	Remote Research Environment
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
ULN	Upper Limit of Normal
UMLS	Unified Medical Language System
WHO	World Health Organization

1 Responsible parties

Table 1-1 Main responsible parties

Role	Person
Main protocol author	[redacted]
Principal investigator (PI)	
Study coordinator	
MAH contact person	

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

v00 – 24 November 2016

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 LCZ696 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 LCZ696, as well as the risks for hypotension, hyperkalemia, hepatotoxicity, and renal impairment, compared to use of ACE 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 LCZ696 (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

To estimate the incidence of all specific safety events (same as above) in HF patients newly starting treatment with LCZ696 without prior exposure to ACEIs or ARBs

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 ACEIs/ARBS)

Exploratory objectives

1. To estimate the relative risk of angioedema in adult HF patients newly starting treatment with LCZ696 (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 LCZ696 (with or without prior ACEI/ ARB exposure) vs. 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 LCZ696 (with or without prior ACEI/ARB exposure) vs. HF patients newly starting treatment with ACEIs (with or without prior ACEI/ARB exposure)

Study design

Cohort study to estimate the incidence and relative risks for angioedema, hypotension, hyperkalaemia, hepatotoxicity, and renal impairment in adult patients diagnosed with HF (prevalent and incident) newly starting LCZ696 or using ACEIs

Population

The overall study population will consist of adult patients (≥ 18 years of age) with prevalent or incident HF initiating either LCZ696 or using an ACEI (no concomitant use of LZC696/ACEI) during the study period identified from five European electronic healthcare databases from Denmark (DK), the Netherlands (NL), Italy (IT), Spain (ES), and the United Kingdom (UK). Except the Danish and the Dutch database, all databases obtain data from general practices. Stratifications will be made for prior use of ACEIs/ARBs.

For each of the databases, the study period starts at the time Entresto® is launched in the country. The end of the study period will be 30 June 2021 at the latest.

The comparator cohort of ACEI HF patients without prior use of ACEIs/ARBs may be small and selective. We may therefore supplement this ACEI comparator cohort with a historical cohort of ACEI initiators who are treatment-naïve to ACEIs using data prior to Entresto® market approval, if needed.

Variables

The primary outcome of interest is angioedema; in addition, hypotension, hyperkalemia, hepatotoxicity, and renal impairment will be studied. The events will be identified by using the database specific coding systems, e.g. Read, International Classification of Diseases (ICD) 9th or 10th revision, or International Classification of Primary Care (ICPC).

The exposures of interest are new treatment with LCZ696 or an ACEI on or after the date of HF diagnosis. 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 12 months 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 12-month look-back period before the index date.

Data sources

All data will be obtained from five European electronic healthcare databases. The following databases will be used:

CPRD (*The Clinical Practice Research Datalink*) from the UK

PHARMO (*The PHARMO Database Network*) from the Netherlands

SIDIAP (*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària*) from Catalonia, Spain

HSD (*Health Search IMS Health Longitudinal Patient Database*) from Italy

Aarhus University Prescription Database and Danish National Patient Registry from Denmark

Study size

It is anticipated, based on estimates from forecasts, that approximately 29,000 LCZ696 initiators may be included in this study with accumulated 24,000 patient-years (PYs) of LCZ696 exposure. This will allow estimating an incidence rate of 5.5/1,000 PYs (assumed for angioedema) with a 95% confidence interval ranging from 4.6 to 6.5 if we observe 132 cases of angioedema. Feasibility assessments will provide information about how many patients initiating ACEIs will possibly be accrued.

Data analysis

Descriptive statistics will be provided as applicable. Incidence rates 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 angioedema.

Milestones

Start of data collection: Q2 2017

End of data collection: After reaching approximately 24,000 patient-years (PYs) of total exposure with LCZ696 in the database(s), but latest 31 Dec 2021

Interim report 1: Q1 2018

Interim report 2: Q1 2019

Interim report 3: Q1 2020

Interim report 4: Q1 2021

Interim report 5: Q1 2022

Registration in the EU PAS register: after protocol endorsement by CHMP/PRAC

Final report of study results: 31 Dec 2022

3 Amendments and updates

Major updates compared to the previous LCZ696B2014 protocol version 0.0 (dated 18-July-2016) include:

- All analyses will be performed in collaboration between [redacted], the scientific lead, and the [redacted], the coordinating centre for the study
- The 'PHARMO Database Network' (PHARMO) will replace the 'Integrated Primary Care Information Project' (IPCI) database as data source for the Netherlands as approved by PRAC
- Reference to the 'EU ADR Alliance' was deleted throughout the protocol, as two databases are not part of the Alliance (CPRD, PHARMO) and the study therefore, will not run under the 'Alliance' umbrella anymore
- Use of data on ethnicity/race as co-variate will be used where possible in a sensitivity analysis (see Section 7.7.1.2.3)
- It was clarified that study objectives in databases with linkage to hospital data (CPRD, SIDIAP, PHARMO) will be assessed both in the full population (i.e. patients with or without linked hospital data available), as well as the sub-group of patients with hospital data linkage, as a stratified analysis (see Section 7.7)

4 Milestones

Table 4-1 PASS Study milestones

Milestone	Planned date
Start of data collection	Q2 2017
End of data collection	After reaching approximately 24,000 patient-years (PYs) of total exposure with LCZ696 in the database(s), but latest 31 Dec 2021
Interim report 1	Q1 2018
Interim report 2	Q1 2019
Interim report 3	Q1 2020
Interim report 4	Q1 2021
Interim report 5	Q1 2022
Registration in the EU PAS register	After endorsement by CHMP/PRAC
Final report of study results	31 December 2022

5 Rationale and background

LCZ696 (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 LCZ696 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 Entresto® (the PARADIGM-HF trial) which included more than 8,400 HF patients with New York Heart Association (NYHA) class II-IV (ejection fraction ≤40%) LCZ696 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 ACE inhibitor (ACEI) enalapril, while showing a similar safety profile as enalapril (McMurray et al 2014).

Based on this pivotal trial, Entresto® was approved in 2015 in the United States, the European Union (EU) and various other countries.

In the EU, 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 LCZ696 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, hyperkalaemia, hepatotoxicity, and renal impairment.

5.1 Angioedema

The majority of the data on the risk for angioedema with LCZ696 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, which was followed by 2.) a single-blind run-in period during which all patients received LCZ696, and 3.) a double-blind treatment phase in which subjects were randomized to either of the study groups (enalapril vs. LCZ696). 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 LCZ696 run-in, 10 patients (0.11%) had adjudication committee-confirmed angioedema events in association with LCZ696.

Confirmed angioedema occurred during the double-blind period in 19 patients (0.45%) in the LCZ696-treated group (n=4,203) and in 10 patients (0.24%) in the enalapril group (n=4,229). Although there were slightly higher rates of angioedema reported for LCZ696 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 LCZ696 (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).

The risk for angioedema associated with LCZ696 in every-day clinical practice is currently unknown and will be investigated in this non-interventional study.

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 LCZ696, 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 incidence rate (IR) of angioedema experienced by ACEI users reported in non-interventional studies (NIS) ranges from 1.6 to 4.4 per 1,000 person-years (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). 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) showed that the angioedema IR for ACEIs can be around 9.7 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 4.76% of LCZ696-treated patients compared with 11.9% and 2.67% of enalapril-treated patients, respectively, with hypotension reported as a serious 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.

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). LCZ696 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 LCZ696- and 14.0% and 21.1% of enalapril-treated patients, respectively.

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

Hyperkalemia may occur with ACEI, ARB 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 LCZ696 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 LCZ696 and 4.4% (n=184) of patients treated with enalapril had adjudicated hepatotoxicity as an AE. The most frequent hepatotoxicity-related AEs that were more frequently reported for subjects in the LCZ696 group as compared to the enalapril group were hepatic steatosis (0.43% vs. 0.50%), ascites (0.36% vs. 0.52%), ALT increased (0.31% vs. 0.14%), AST increased (0.31% vs. 0.05%) and International Normalized Ratio (INR) increased (0.26% vs. 0.50%).

Hepatotoxicity is included in the 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 LCZ696. In the double-blind period of PARADIGM-HF, renal impairment was reported in 10.1% of LCZ696- and 11.5% of enalapril-treated patients.

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 LCZ696 versus ACEI use in adult patients with HF.

The study objectives are listed below.

6.1 Primary objective

1. To estimate the incidence of specific safety events of interest in HF patients newly starting treatment with LCZ696 (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 assess the incidence of all specific safety events (as mentioned above) in HF patients newly starting treatment with LCZ696 without prior exposure to ACEIs or ARBs

6.2 Secondary objectives

1. To assess 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 assess 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 assess the relative risk of angioedema in adult HF patients newly starting treatment with LCZ696 (without prior ACEI/ ARB exposure) as compared to adult HF patients newly starting treatment with ACEIs (without prior ACEI/ARB exposure)
2. To assess the relative risk of angioedema in adult HF patients newly starting treatment with LCZ696 (with or without prior ACEI/ ARB exposure) vs. HF patients newly starting treatment with ACEIs (without prior ACEI/ARB exposure)
3. To assess the relative risk of angioedema in adult HF patients newly starting treatment with LCZ696 (with or without prior ACEI/ARB exposure) vs. HF with ACEI exposure (with or without 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 will be 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 LCZ696 (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. As various safety events of interest are the major outcomes of interest of this study, it qualifies as a (non-imposed) non-interventional post-authorization safety study (PASS).

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, renal impairment) in patients newly starting LCZ696 (incident users), we will identify an initial cohort of all LCZ696 initiators (regardless of prior exposure to ACEIs or ARBs) with patient accrual beginning at the specific launch date of Entresto® (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, we will identify an initial contemporaneous comparator cohort of ACEI initiators. Data collection will end when the necessary sample size of 24,000 patient-years (PYs) has been reached (see Section 7.5 'Study size/power calculation'), but on 31 December 2021 at the latest (even in case 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 ACEI users. Entresto® will be newly introduced to the market and the cohort of users will therefore automatically consist of new users. As indicated in the Entresto® '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 LCZ696 with an ACEI is contraindicated due to the increased risk of angioedema. LCZ696 must not be initiated until 36 hours after taking the last dose of ACEI therapy.

Since the majority of LCZ696 users are expected to have been treated with an ACEI or ARB before starting LCZ696, these patients will likely have a low baseline risk of angioedema as susceptible patients have been depleted. ACEI initiators who are treatment-naïve to ACEIs and ARBs however, will 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 LCZ696 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 favour of LCZ696. Therefore, it is considered that the optimal comparison is between LCZ696 initiators who are treatment naïve to ACEIs/ARBs against ACEI initiators without prior ACEI/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 LCZ696 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 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 HF-rEF (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 HF-rEF (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. We may therefore 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. In addition, to explore the impact of depletion of susceptibles we will also assess the rate of events in users of ACEIs with prior use of ACEIs/ARBs.

7.1.2 Feasibility assessments

The above outlined inclusion of a historical cohort of ACEI users could lead to bias if these patients are systematically different from contemporaneous users. Thus, as part of the feasibility assessments, we will describe the demographic and clinical characteristics of HF patients initiating ACEI treatment who are treatment-naïve to ACEIs and ARBs annually over the historical period. These results will provide a general assessment of whether any ascertained patient characteristic has systematically changed throughout the historical period and whether the historical control cohort may be systematically different from the contemporaneous control cohort. Understanding both of these aspects will inform confounder selection (with regard to channelling) for the comparative assessment of the relative risk of angioedema.

7.2 Setting

7.2.1 Source population

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

- the 'Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) from Catalonia, Spain
- the 'PHARMO Database Network' (PHARMO) from the Netherlands
- the 'Health Search IMS Health Longitudinal Patient Database' (HSD) from Italy
- the 'Aarhus University Prescription Database' and Danish National Patient Registry from Denmark
- the Clinical Practice Research Datalink (CPRD) from the UK

7.2.2 Study population

The overall study population will consist of adult patients (≥ 18 years of age) with HF initiating either LCZ696 or using an ACEI during the study period.

We will identify HF patients using both recorded inpatient and outpatient diagnoses based on the specific coding system used by the individual database (e.g. READ in CPRD, ICD-9 in HSD, ICD-10 in SIDIAP, PHARMO, Aarhus University Prescription Database and the Danish National Patient Registry, and International Classification of Primary Care codes [ICPC] 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 Entresto® launch dates in the countries of interest (see launch dates in Table 7-1 below) and will end 30 June 2021 the latest. Historical ACEI initiators will be identified starting 01 January 2011. The total study time frame (including the beginning of the 12 months look-back period before cohort entry) will begin in 01 January 2010 the earliest.

Table 7-1 Entresto® launch date in the countries of interest

Country	Launch date
Denmark	December 2015
Italy	April 2016
Netherlands	July 2016
Spain	October 2016
United Kingdom	December 2015

7.2.4 Inclusion and exclusion criteria

Inclusion criteria

Patients will be required to:

- Have a recorded diagnosis of HF in the database during the period of follow-up or look-back period, prior to the first prescription of LCZ696 or ACEI or a diagnosis for HF within three months after initiating treatment
- Be aged ≥ 18 years at the time of the first prescription (or pharmacy fill) for LCZ696 or an ACEI
- Have ≥ 12 months of valid database history prior to the first prescription (or pharmacy dispense) for LCZ696 or an ACEI (i.e. the patient was registered in the database for at least one year)
- Have non-missing data on age and sex
- Are still followed in the database at the start of the study period
- Additionally, for patients initiating ACEIs: Have no recorded prescription or pharmacy fill for an ACEI and ARB within a 12-month pre-index period

Exclusion criteria

Use of LCZ696 by patients with prior angioedema history is contraindicated; patients with a recorded angioedema diagnosis prior to the index date (see Section 7.2.5 for definition of 'index date') are excluded from all cohorts.

Patients with a recorded history of chronic hepatic disease prior to the index date will be excluded for the assessment of 'hepatotoxicity', and accordingly, patients with a recorded history of chronic renal disease for the assessment of 'renal impairment', respectively.

7.2.5 Cohort start

The date of the first recorded prescription (or pharmacy fill) for LCZ696 or ACEI in the study period will be defined as the cohort entry (= start of follow-up or 'index date'). A look-back period of 12 months is used to determine baseline characteristics.

7.2.6 Follow-up

Eligible patients will be followed up 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:

- If they discontinue their LCZ696 or ACEI treatment;
- Add treatment with a RAAS blocking agent (i.e. add-on of an ACEI [only for initiators of LCZ696], an ARB, or aliskiren);
- Switch initial treatment to a RAAS blocking agent (i.e., LCZ696 to an ACEI, ARB or aliskiren, ACEI to LCZ696, an ARB, or aliskiren [switching within the ACEI class however, will not be censored]);
- The patient stops contributing data to the database (e.g. patient dies, or leaves the practice, etc.);

whichever occurs 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 LCZ696, 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]/Multilex 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. Episodes of treatment will be created for LCZ696 and for ACEIs/ARBs for all prescriptions in the same group if they are less than 90 days between end of previous prescription and the start of the new prescription. 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 have a prescription or pharmacy fill for an ACEI or ARB recorded within 12 months before cohort entry, 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 case, follow-up ends before the 90 days are over a patient will not be considered to have discontinued.

We will define five different exposure groups (cohorts): two for LCZ696-, and three for ACEI-users.

7.3.1.1 LCZ696 user cohorts

7.3.1.1.1 LCZ696 initiators regardless of prior ACEI/ARB use (cohort 1)

This group will include all patients fulfilling the inclusion criteria (Section 7.2.4) who start using LCZ696 during the study period – regardless of prior exposure to ACEIs or ARBs.

7.3.1.1.2 LCZ696 initiators treatment naïve to ACEIs/ARBs (cohort 2)

Cohort 2 is the subset of cohort 1 without prior use of ACEI/ARBs in the 12 months prior.

7.3.1.2 ACEI user groups

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

This group will include all patients fulfilling the inclusion criteria (Section 7.2.4) who use ACEIs during the study period – regardless of prior exposure to ACEIs or ARBs.

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

Cohort 4 is the subset of cohort 3 without use of ACEI/ARB in the 12 months prior.

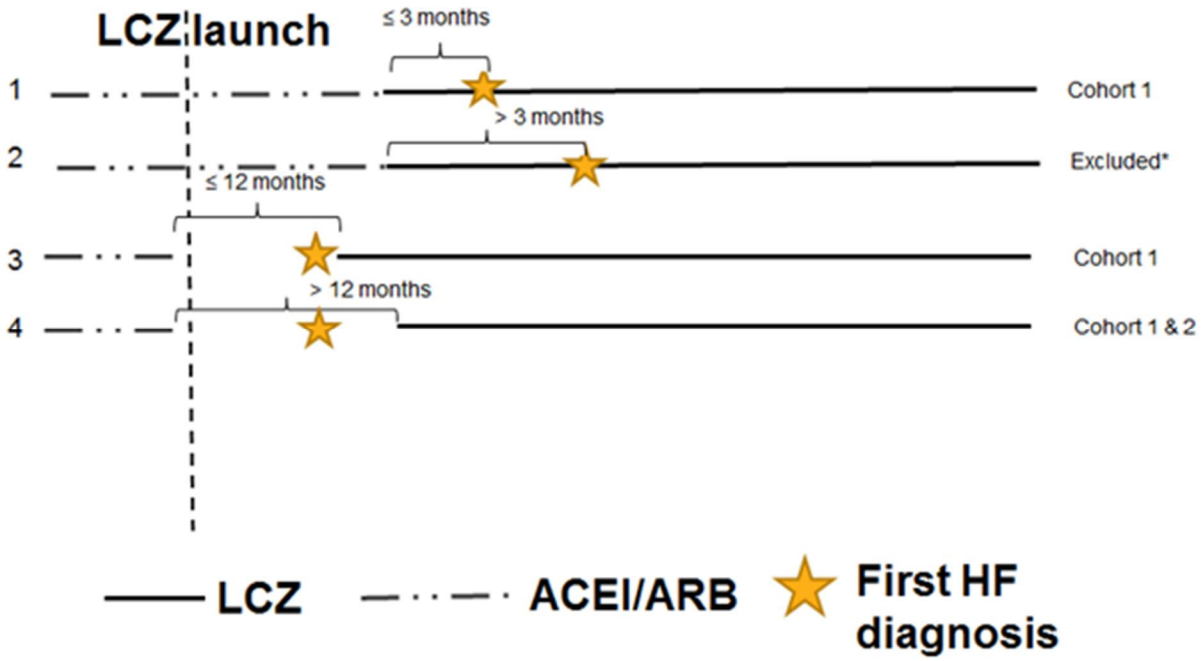
7.3.1.2.3 ACEIs – Historical naïve to prior ACEI/ARB use (cohort 5)

This group will include all patients fulfilling the inclusion criteria (Section 7.2.4) who initiate ACEIs between 1/1/2011 and the start of the study peri od – and have not used ACEIs or ARBs in the 12 months prior.

This cohort 5 will only be used if there are not enough subjects in cohort 4.

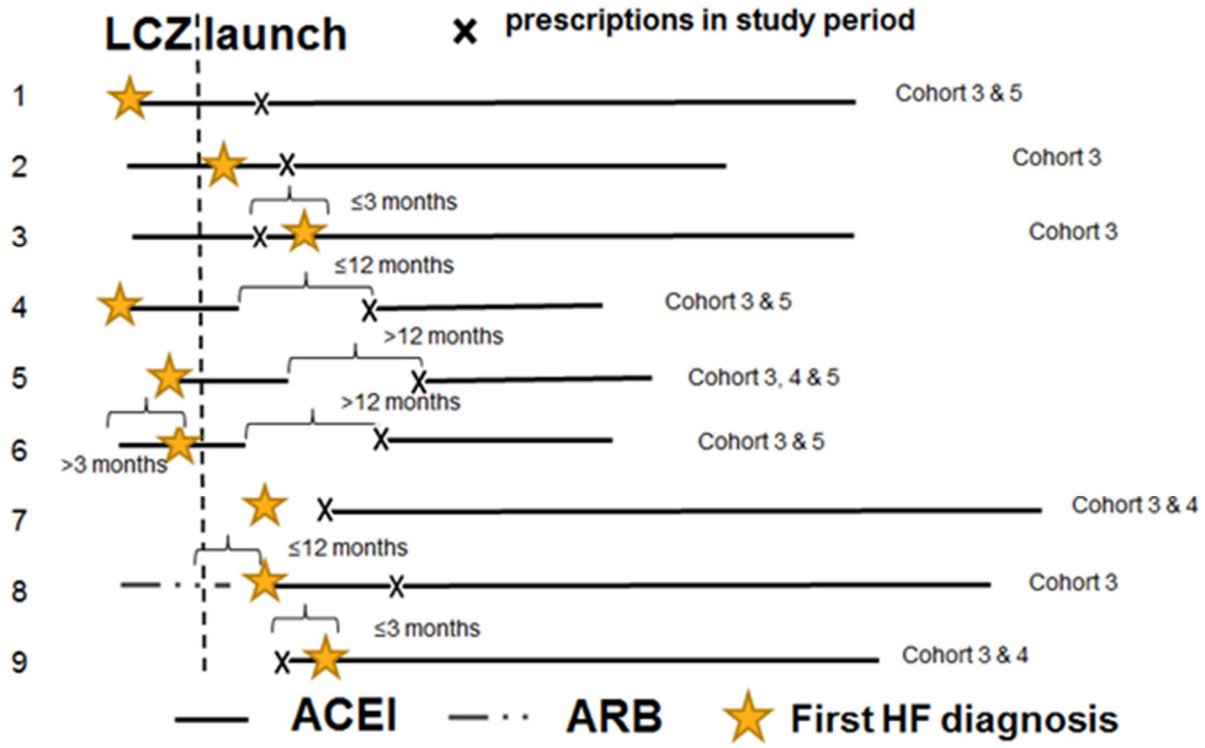
Figure 7-1 below illustrates cohort allocation and start of follow-up based on various exposure scenarios for LCZ696 and Figure 7-2 for prevalent ACEI users.

Figure 7-1 Start of follow-up in LCZ696 initiators (with or without prior ACEI/ARB use)



Heart failure diagnosis must be recorded either prior or within 3 months after initiating treatment

Figure 7-2 Start of follow-up in prevalent ACEI users



Heart failure diagnosis must be recorded either prior or within 3 months after initiating treatment

Table 7-2 provides an overview of the use of the above detailed sub-groups by study objective.

Table 7-2 Study exposure subcohorts, by study objective

Study objective	Subcohorts			
	Cohort 1 (any LCZ696)	Cohort 2 (LCZ696, no prior ACEI/ARB)	Cohort 3 (any ACEI)	Cohort 4 (ACEI, no prior ACEI/ARB)
Primary, no 1 (incidence rates of specific safety events of interest in HF patients newly starting treatment with LCZ696 [regardless of prior use of ACEIs or ARBs])	✓	--	--	--
Primary, no 2 (incidence rates of specific safety events in HF patients newly starting treatment with LCZ696 [without prior exposure to ACEIs or ARBs])	--	✓	--	--
Secondary, no 1 (incidence rates specific safety events in HF patients newly starting treatment with ACEIs	--	--	--	✓

[without prior exposure of ACEIs/ARBs])				
Secondary, no 2 (incidence rates 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 LCZ696 [without prior ACEI/ ARB exposure]) compared to adult HF patients newly starting treatment with ACEIs [without prior ACEI/ARB exposure])	--	✓	--	✓
Exploratory, no 2 (RR assessment of angioedema in adult HF patients newly starting treatment with LCZ696 [with or without prior ACEI/ ARB exposure]) vs. 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 LCZ696 [with or without prior ACEI/ARB exposure] vs. HF with ACEI exposure [with or without prior ACEI/ARB exposure])	✓	--	✓	--

Note: cohort 5 is added to cohort 4 if the number of subjects in cohort 4 is insufficient

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

7.3.2 Safety events of interest

The safety events of interest include a recorded diagnosis of:

- Angioedema (primary event of interest)
- Hypotension
- Hyperkalemia
- Hepatotoxicity
- Renal impairment

as identified from in- or outpatient electronic medical records.

Recorded abnormal laboratory values (for identification of hyperkalemia, renal impairment, or hepatotoxicity) or other measurements (e.g. blood pressure) will also be included for identification of outcomes of interest if available.

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, or ICD-10, ICPC). An initial list of terms that would be used for the event definition mapping is supplied in Annex 12.3.

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 the cases.

Code lists and identification algorithms (e.g. with confirmatory treatments such as corticosteroids, epinephrine or antihistamines) will be created upon completion of the protocol, in close collaboration with the participating databases and be described in the statistical analysis plan (SAP). Detailed knowledge of the healthcare system is necessary to provide the correct definitions.

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

Table 7-3 provides information on the available components by database to identify angioedema events.

Table 7-3 Components for the identification of angioedema in the databases

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

CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; 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

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 on standing (Robertson 2008).

Code lists and identification algorithms will need to be created using a code-mapping programme, in close collaboration of the participating databases and be described in the SAP. Detailed knowledge of the healthcare system is necessary to provide the correct definitions.

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)**
Codes	ICPC/ICD-10	ICD-9	ICD-10	READ	ICD-9/10
Blood pressure	Yes	Yes	No	Yes	Yes
Text / symptoms	Yes	No	No	No	No

CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; 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

Note: details on databases, see Section 7.4

7.3.2.3 Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration > 5 mmol/L (Evans et al 2005). Code lists will need to be created using a code-mapping programme upon completion of the protocol, in close collaboration of the participating databases and 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 provides information on the available components by database to identify events of hypotension.

Table 7-5 Components for the identification of hyperkalemia in the databases

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

CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; 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

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). Detailed code lists will be created using a code-mapping program and 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 provides information on the available components by database to identify events of hepatotoxicity.

Table 7-6 Components for the identification of hepatotoxicity in the databases

	Database (country)				
	PHARMO (NL)	**HSD (IT)**	**Aarhus (DK)**	**CPRD (UK)**	**SIDIAP (ES)**
Codes	ICPC/ICD-10	ICD-9	ICD-10	READ	ICD-9/10
Laboratory (AST/ALT)	Yes	Yes	Yes	Yes	Yes
Text / symptoms	Yes	No	No	No	No

ALT = alanine aminotransferase; ALP = alkaline phosphatase; CPRD = Clinical Practice Research Datalink; DK = Denmark; 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

Note: details on databases, see Section 7.4

7.3.2.5 Renal impairment (acute kidney injury)

Acute renal impairment, or acute kidney injury is characterised 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

Code lists will need to be created using a code-mapping program and 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)**
Codes	ICPC/ICD-10	ICD-9	ICD-10	READ	ICD-9/10

Laboratory (creatinine)	Yes	Yes	No	Yes	Yes
Text / symptoms	Yes	No	No	No	No

CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; 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

Note: details on databases, see Section 7.4

7.3.3 Patient characteristics/demographics

We will summarize patient characteristics at the cohort entry date, including:

- Age (continuous, categorical)
- Sex
- Ethnicity (only available in CPRD, but recording rather incomplete [Mathur et al 2014])
- Comorbidities (i.e. diseases/conditions already prevalent at the index date or which occurred or were recorded within 12 months prior to the index date), e.g.
  - Hypertension
  - Myocardial infarction
  - Stroke or transient ischemic attack
  - 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)
  - Others (to be discussed)
- Comedication to the index date, e.g.:
  - ACEIs and/or ARBs
  - Beta-blockers
  - Calcium channel blockers
  - Mineralocorticoid receptor antagonists (MRAs)
  - Diuretics (thiazides, loop, potassium-sparing diuretics, others [excluding MRAs])
  - Digoxin
  - Nitrates
  - Hydralazine
  - Antiarrhythmic agents
  - Anticoagulants
  - Antiplatelets (including prescription aspirin)
  - Lipid lowering drugs
  - Antidiabetics (including DPP-4 inhibitors)

Prescription non-steroidal anti-inflammatory drugs (NSAIDs)

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

Number of medicines prescribed from different ATC codes (in the year prior to the index date);

Number of visits/contacts with cardiologists ('consultation rate - specialist', in the year prior to the index date);

Number of visits/contacts with general practitioner (GP) ('consultation rate - GP', in the year prior to the index date).

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

7.4 Data sources

This study will be conducted by using European databases that comprise 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 LCZ696.

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 IMS Health Longitudinal Patient Database (HSD) from Italy provided by Società Italiana di Medicina Generale, the PHARMO Database Network from the Netherlands provided by the PHARMO Institute for Drug Outcomes Research, and the Aarhus University Prescription Database and Danish National Patient Registry from Denmark provided by Aarhus University.

All analyses will be performed in collaboration between [redacted], and the [redacted] according to contractual agreements.

Table 7-8 provides an overview of database characteristics including the available data. These databases have a mean follow-up ranging from 2.5 to 11 years. The databases are representative of the country-specific populations in terms of age and gender. The databases that will be 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 five databases will be approximately 16 million in 2016.

Table 7-8 Overview of databases to be used for the study

	Database				
Characteristic	**PHARMO**	**CPRD**	**Aarhus**	**HSD**	**SIDIAP**
Country	Netherlands	United Kingdom	Denmark	Italy	Spain (Catalonia)

	Database				
Characteristic	**PHARMO**	**CPRD**	**Aarhus**	**HSD**	**SIDIAP**
Type of database	EMR	EMR	ADM	EMR	EMR
Number of patients, millions	1.2*	5.7 (approx. 55% linked to HES data)	1.8	1.5	5.1 (1.7 linked to hospital data)
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Date of death	Yes	Yes	Yes	Yes	Yes
Cause of death	No	Yes	Yes	No	No
Updates	Annual (October)	3-times a year	Yearly (April)	2-times a year: (30/06 and 31/12)	Yearly (April/May)
Prescriptions					
Outpatient Rx	Yes	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes (specialist incomplete)
Coding of drugs	ATC	BNF/Multilex code	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	Yes
Outcomes					
Hospitalizations	Yes	Yes	Yes	Yes	Yes (for 1.7 mio linked patients)
Outpatient diagnoses	Yes	Yes	Yes	Yes	Yes
Coding of disease	ICPC, ICD-10	READ (ICD-10 for HES data)	ICD-10	ICD-9 CM	ICD-10 (ICD-9 for hospital data)

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; EMR = Electronic Medical Records; ICD= International Classification of Disease, ICPC = International Classification of Primary Care

* GP and out-patient pharmacy data

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).

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 the 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 feed back 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. Validation of data with original records (specialist letters) is also available.

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 upon 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 summary (date and Read codes), hospital clinic summary, preventive treatment and immunizations, death (date and cause). For a proportion of the CPRD panel practices (~55%), the GPs have agreed to permit CPRD to link at patient level to the Hospital Episode Statistics (HES) data.

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 classification), and related procedures (coded using the ICD-10 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).

CPRD is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

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 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.

SIDIAP is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

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 1 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. The HSD has been used as data source 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 prescription dosage is also imputed by GPs.

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

HSD is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

7.4.4 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 out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. Detailed

information on the methodology and the validation of the used record linkage method 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. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data 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. 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.

The General Practitioner (GP) Database comprises 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 WHO Anatomical Therapeutic Chemical (ATC) Classification System. Diagnoses and symptoms are coded according to the International Classification of Primary Care (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 the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (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 WHO International Classification of Diseases (ICD) 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.

PHARMO is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

7.4.5 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 and the population can also be linked to other National Danish registries. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on 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).

Aarhus is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

7.5 Study size/power calculation

Since the primary objective of the study is to estimate the incidence rate (IR) of angioedema and other events of interest with LCZ696, we provide in Figure 7-3 the confidence intervals (CIs) that we expect for angioedema, the rarest of all the events, given different sample sizes. We assumed an incidence rate of angioedema following LCZ696 of 5.5/1,000 PYs, based on an incidence rate 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 assuming an incidence rate ratio LCZ696/ACEI of 1.9, based on the results of the double-blind part of the pivotal phase III study PARADIGM (McMurray et al 2014). We also provide in Figure 7-4 the confidence intervals that we expect for the hazard ratio (HR) of LCZ696 vs ACEI for angioedema (exploratory objective [see Section 6.3]) for different sample sizes. Additionally to the previous assumptions on LCZ696 and ACEI incidence rates, we also assumed to have the same exposure for LCZ696 and ACEIs.

With these assumptions, we aim to have approximately 24,000 PY of exposure with LCZ696, which will provide an estimated incidence rate 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 following LCZ696

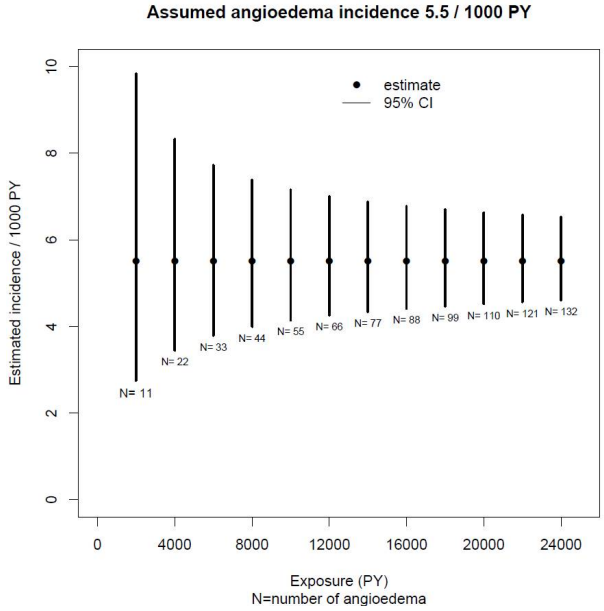


Figure 7-4 Examples of confidence intervals for the hazard ratio (HR) of angioedema following LCZ696 vs ACEI

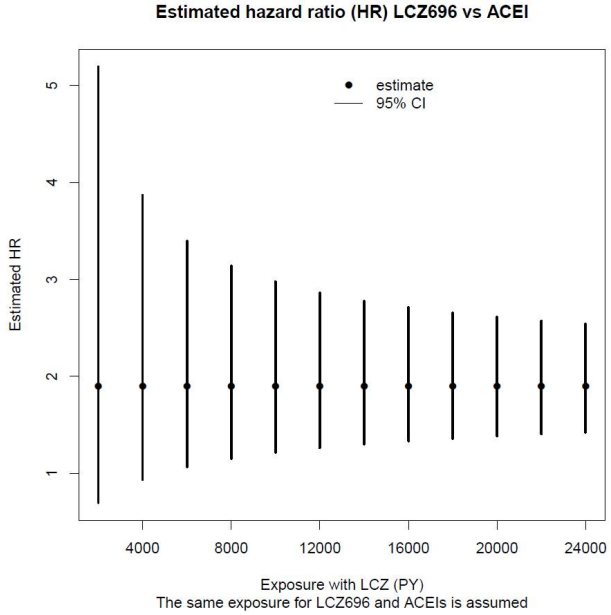


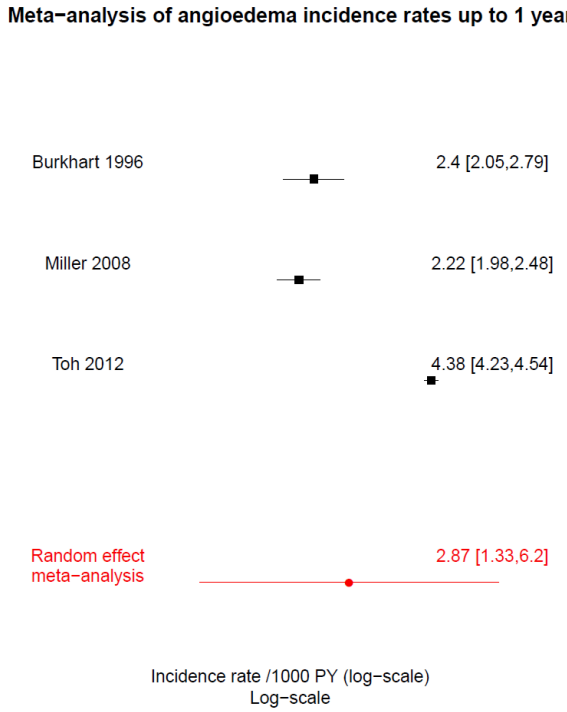
Table 7-9 Literature information for the meta-analysis of angioedema incidence rate following ACEIs

Reference	Data source	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 following ACEI



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

It is anticipated that approximately 29,000 LCZ696 initiators may be included in this study (approximately 25,000 patients from the three databases outlined in Table 7-10 until Q2 2021, and approximately another estimated 4,000 patients from the Dutch and Danish databases overall). Based on this forecast, we are confident that we will be able to include 24,000 PYs of LCZ696 exposure across all databases (assuming at least an average of about 10 months of LCZ696-exposed person-years of follow-up).

Assuming that 10% of LCZ6969 initiators will be naïve to ACEI/ARB treatment, it is expected that approximately 2,900 ACEI/ARB naïve LCZ696 initiators may be included (details on forecasts are provided in Table 7-10). The feasibility assessments will provide information about how many patients initiating ACEIs (without prior ACEI) will possibly be accrued.

Table 7-10 Forecasts of the cumulative number of LCZ696 exposed patients in three European databases of interest based on country-wide LCZ696 exposure estimates and database coverage

	2016	2017	2018	2019	2020	2021
SIDIAP (Spain)	261	1,251	3,427	6,610	9,226	12,638
CPRD (UK)	197	1,313	4,013	7,951	10,766	14,699
HSD (Italy)	41	378	968	1,406	1,740	2,288
Total LZC696 initiators in 3 DBs	*499*	*2,942*	*8,408*	*15,967*	*21,732*	*29,625*
Assuming that 10% of LCZ696 initiators are ACEI-/ARB-treatment naïve	*50*	*294*	*841*	*1,597*	*2,173*	*2,963*

CPRD = Clinical Practice Research Datalink; DB = database; HSD = Health Search CSD Longitudinal Patient Database; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; UK = United Kingdom

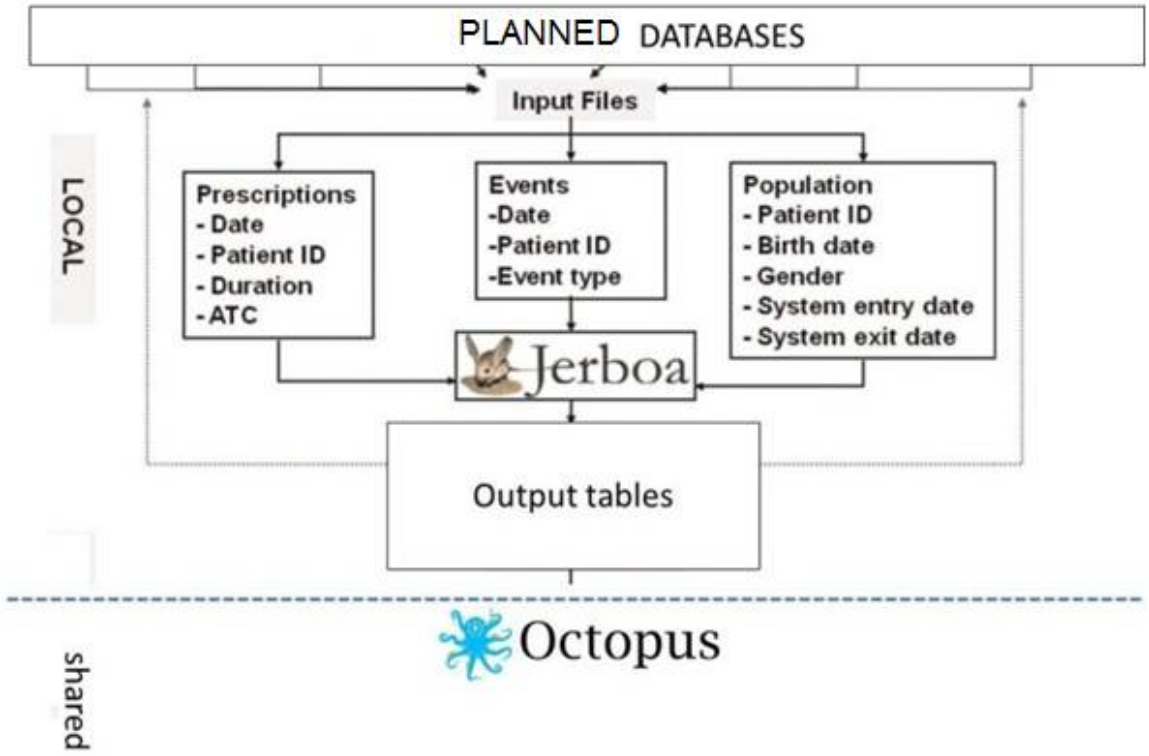
Database coverage: CPRD: approximately 8.3% of overall UK population; SIDIAP: approximately 11.4% of overall population in Spain, HSD: approximately 1.7% of overall population in Italy

No forecasts available for the Netherlands and Denmark; similar patient counts are expected for PHARMO (NL) and Aarhus (DK) as for HSD (Italy)

7.6 Data management

Data extraction and elaboration will be done locally and pooling of aggregated data is done on a Remote Research Environment (see Figure 7-5 for overview).

Figure 7-6 Model for data sharing and elaboration



Due to the different database characteristics and coding schemes it is not possible to use one single data extraction algorithm for all the databases. To reconcile differences across terminologies a shared semantic foundation will be built for the definition of events under study by selecting disease concepts from the Unified Medical Language System (UMLS, and set up a multi-step and iterative process for the harmonization of event data (Trifiro et al 2014). The sequential steps of this process are shortly described below:

All events/outcomes, risk factors or potential confounder, will be ascertained using a list of agreed ICD (Denmark, Italy, Netherlands and Spain), ICPC (Netherlands) and READ (UK) codes. The proposed lists of codes will be created following a number of steps:

- Case definition
- Preliminary list of concept identifiers using a code-mapper to UMLS Meta-thesaurus Browser;
- Addition of codes found after literature review of validated lists of codes for each of the study outcomes in each of the databases; and
- Consensus with partners involved in the management and analysis of each of the 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 specific incidence rates, according to standard quality assurance procedures (see below)

Identification of Unified Medical Language System® (UMLS®) concepts

A UMLS concept is identified by a Concept Unique Identifier (CUI) and describes a single medical notion that can be expressed using different synonyms (terms). For each event, a medical definition will be created and, based on such definition relevant UMLS concepts are identified and projected into the database-specific terminologies. In addition, for those databases where free text is available, the labels of the codes are considered for free text search of the events.

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 event based on the consensus of the data providers. This data extraction algorithm will then be implemented by all databases.

Event data extraction

Subsequently, each database 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 endpoint and covariate we benchmark database-specific incidence rates (IRs) using Jerboa©, scripts in a quality run. The observed IRs are compared with 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 (see Trifiro et al 2014). It maximizes the involvement of the data providers 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 study endpoints will be created by the local data processors based on Jerboa instructions.

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

Data elaboration

A standardized Jerboa© script and instructions will be created by [redacted] to create the study specific output tables. This will be double coded in SAS (version 9.4) by the [redacted].

7.6.1 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 as it provides unbiased estimates.Lack of information on risk factors such as smoking, or the use of certain drugs may occur, but this is unlikely differential.

7.6.2 Data sharing

A study-specific folder on the central Octopus remote research environment (RRE) for secure access by members will be used to analyse the output provided by Jerboa©. These output files will contain only anonymized de-identifiable data that will be shared in the RRE where members will have a secure and restricted access and where data will be analysed. SAS, version 9.4, will be used for post-processing of data.

7.7 Data analysis

All analyses will be performed in collaboration between [redacted] the scientific lead, and the [redacted], the coordinating centre for this multi-database study. Data will be deposited in the Remote Research Environment and participating partners can inspect the analysis by remotely accessing.

Linkage to hospital data is used where feasible (CPRD, SIDIAP, PHARMO) to supplement the basic datasets that include the regular data available from the databases. In these databases, the study objectives will be assessed in the full population (with our without linkage), and – as a stratified analysis – also in the sub-group 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 will be provided in the SAP and be prepared after PRAC approval of the protocol.

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 based on data until 31 Dec 2016. Data will be available in all databases with a delay of approximately 6 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). The first interim report is planned to be submitted in Q1 2018.

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 incidence rates will be made available only 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 through 31 Dec 2021 (or earlier if the necessary number of LCZ696 initiators is achieved before).

7.7.1.2.1 Demographic and baseline characteristics of exposure cohorts

Demographic and baseline clinical characteristics of study patients initiating LCZ696 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 individual database.

Differences in demographic and baseline characteristics of LCZ696 and ACEI initiators will be assessed via the non-parametric Wilcoxon-Mann-Whitney-Test for continuous variables, and the Chi-square test for categorical variables. A cross tabulation of age groups and sex will be provided for LCZ696 and ACEI initiators.

A flow chart of cohort attrition will be provided. 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 Entresto® for patients previously using ACEI who are started on LCZ696 in actual clinical care setting as requested by PRAC. The current proposal is to assess (i) the proportion of LCZ696 patients for which there is no evidence indicating concurrent use during the 36-hour period, and (ii) the proportion of LCZ696 users with concurrent prescriptions (i.e. on the same day) of ACEI and LCZ696 indicating non-adherence to the 36-hour wash-out period (see also Section 7.10).

7.7.1.2.2 Primary, secondary and exploratory analyses

Primary analysis

We will separately estimate the risk of the outcomes of interest (i.e. angioedema [primary endpoint], hypotension, hyperkalaemia, hepatotoxicity, renal impairment) as incidence rates (IRs), i.e. as the number of events of interest divided by person-time, along with 95% confidence intervals (CIs) in cohorts 1-2 (by database and pooled using a meta-analytical approach [details will be provided in the statistical analysis plan [SAP]):

1. Cohort 1: HF patients newly starting treatment with LCZ696 (regardless of prior use of ACEIs or ARBs)
2. Cohort 2: in the sub-population of HF patients newly starting treatment with LCZ696 without prior exposure to ACEIs or ARBs.
3. IRs will be calculated by the week since cohort entry to allow for inspection of changes over time.

In addition, we will estimate incidence rates 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 analysis

We will estimate IRs (with 95% CIs) and cumulative incidences (for angioedema only) of the outcomes of interest 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 incidence rates 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 (equal to the primary analysis, above).

In a subset of patients from cohort 3 (prevalent ACEI users at cohort entry), we will conduct a sensitivity analysis to calculate the incidence rate taking various different prevalent ACEI exposure periods prior to the index date into account.

Exploratory analyses

Adjusted relative risks for the outcomes of interest will be estimated as hazard ratios (HRs) with 95% CIs among new users of LCZ696, (a) who are treatment-naïve to ACEIs and ARBs, and (b) separately, in LCZ696 initiators regardless of prior ACEI or ARB use, relative to new users of ACEIs (treatment-naïve to ACEIs) by using Cox regression models.

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 (predefined) co-variates for cohort 3 and 4 vs cohort 1.

For the exploratory analyses we will adjust for the PS to limit confounding or potential channelling by matching on PS (in strata), as an addition to confounder control in multivariable regression models.

7.7.1.2.3 Sensitivity analyses

Details on sensitivity analyses will be specified in the SAP, including potential misclassification of initial LCZ696 exposure, referrals to specialists, and confounding factors (including information on race/ethnicity as a co-variate where possible).

7.7.1.2.4 Handling of missing data

Since the underlying data represent attended medical care we assume that absence of information of clinical events means absence of that condition. Lack of information on smoking, and alcohol use may occur, but this is unlikely differential.

7.8 Quality control

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 database partners have experience in conducting pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology; In addition; the 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. Only 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 about the uptake of Entresto®, which may decrease the precision of the estimates from the study. In addition, we expect major issues with the number and selection of the LCZ696 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. If the ACEI/ARB treatment-naïve cohort 4 is too small, a historic cohort will be used (cohort 5), which may have different outcome rates due to different time diagnostic/recording habits over time.

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.

All of the databases, apart from the Aarhus University Prescription Database and PHARMO, have information on prescription only and not on dispensing. None of the databases have data on actual drug intake. This implies that we do not know whether the patient actually took the drug – however, it is known that adherence to drugs is highest at initiation of therapy. Thus, the risk of exposure misclassification is of less concern in the new user design applied.

LCZ696 treatment is likely to be initiated by specialists. Given that most of the databases in the study obtain their data from primary care, prescriptions may be missed. Given that angioedema is more likely to occur shortly after treatment initiation, exposure misclassification may bias the results. Each of the databases will carefully assess how this type of bias can be mitigated, i.e. by verifying prescription durations or by looking at referrals to specialists in the year prior. Sensitivity analyses will be conducted that would exclude subjects for whom we are uncertain about LCZ696 treatment start. Details will be specified in the statistical analysis plan.

There is also a risk that prescribing of LCZ696 may be channelled 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 Entresto® for treatment of chronic HF-rEF 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 may not be available across all databases and proxy measures for HF severity

may not fully address this kind of channelling 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, LCZ696 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 LCZ696 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 LCZ696 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 LCZ696 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 LCZ696. For that reason, we chose to have the comparison of LCZ696 initiators who are treatment naïve to ACEIs/ARBs vs ACEI/ARB treatment-naïve ACEI initiators as the primary exploratory analysis, since we consider this the most accurate comparison. The size of that cohort may however, be limited which is the reason why we considered to also include a historical group of ACEI/ARB treatment-naïve ACEI initiators. Part of the feasibility assessment will also assess if these historical ACEI/ARB treatment-naïve ACEI users (cohort 5) are systematically different from contemporaneous ACEI/ARB treatment-naïve ACEI users from cohort 4.

A comparison of LCZ696 users with prevalent ACEI users would likely bias against LCZ696, as in the group of prevalent ACEI users, the angioedema risk can be expected to be relatively low, as patients with prior ACEI-associated angioedema should not be included and patients with longer-term ACEI exposure have a much lower risk as compared to new ACEI users (see also Section 7.1.1).

Misclassification of endpoints 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 pharmacoepidemiological research. For those databases where free text is available (PHARMO, HSD, CPRD and SIDIAP), validation of endpoints will be conducted and comparison of incidence rates of endpoints among databases in the quality run will allow checking for internal and external validity.

For all databases, apart from Aarhus University Prescription Database, it should be noted that the primary aim of data collection is patient management 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 only databases that capture all prescriptions (primary and secondary care) are Aarhus and PHARMO. 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.

Some of the databases (Aarhus, and SIDIAP) have a mean follow-up of 2.5-6 years hindering the conduct of long-term follow-up studies.

Finally, there are differences in timing of data updates in the various databases (medical records are continuously updated, administrative databases are updated only 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 PRAC, Novartis committed to investigate the 36-hour washout period recommended in the SmPC of Entresto® for patients previously using ACEI who are started on LCZ696 in actual clinical care setting. This washout-period should lower the risk of angioedema potentially caused in patients 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 are currently assessing how to optimally implement this research question.

The current proposal is to assess (i) the proportion of LCZ696 patients for which there is no evidence indicating concurrent use during the 36-hour period, and (ii) the proportion of LCZ696 users with concurrent prescriptions (i.e. on the same day) of ACEI and LCZ696 indicating non-adherence to the 36-hour wash-out period.

8 Protection of human subjects

For this study, participants from various EU member states will process personal data from individuals which is 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 already 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 non identifiable data with less detailed information that will be pooled across databases.

The output files are stored in the central Remote Research Environment (RRE) of the [redacted]. 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. Starting from this, the RRE implements further security measures in order to ensure a high level of stored data protection, according to the article 34 of legislative decree 196/2003 and article 22 of Regulation (EC) 45/2001.

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, UK, Denmark and Italy. 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 sa fety relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and an outcome. 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, the 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 authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation 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]	☒	☐	☐	13
1.1.2 End of data collection[2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☒	☐	☐	13
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

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	☒	☐	☐	13-17

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
management plan, an emerging safety issue)				
2.1.2 The objective(s) of the study?	☒	☐	☐	17, 18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20, 21
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, randomised controlled trial, new or alternative design)	☒	☐	☐	18, 19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	25-29
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)	☒	☐	☐	42

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	20
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	20
4.2.2 Age and sex?	☒	☐	☐	20
4.2.3 Country of origin?	☒	☐	☐	20
4.2.4 Disease/indication?	☒	☐	☐	20
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	20-21

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)	☒	☐	☐	22-25
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)	☒	☐	☐	43, 44
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	22
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?	☒	☐	☐	25-29
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	26, 39, 45

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g.				

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	19, 39, 42, 43
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	43

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.)	☒	☐	☐	22, 29-35
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.)	☒	☐	☐	29-35
8.1.3 Covariates?	☒	☐	☐	29-35
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)	☒	☐	☐	29-35
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	29-35
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	29-35
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	20, 31
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	31
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	31
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	30-35

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	35-38

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?	☒	☐	☐	40
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	38-40
11.3 Are methods of quality assurance described?	☒	☐	☐	43
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☐	30-35, 43-45
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)**

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)	☒	☐	☐	43-45
12.3 Does the protocol address other limitations?	☒	☐	☐	43-45

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?	☒	☐	☐	46
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	45-46

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

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)?	☒	☐	☐	47
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	47

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/-10/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 (broader 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 angieodema (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	Hyperkalaemia, 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