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Quantitative Safety and Epidemiology

Non-Interventional Study Protocol

REDACTED PROTOCOL

LCZ696B2015

Title	Non-interventional post-authorization multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of sacubitril/valsartan (Entresto®)
Protocol version identifier	v00
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Medicinal product	Entresto®
Product reference	EMEA/H/C/004062
Procedure number	EMEA/H/C/004062/MEA/004
Name of Marketing authorization holder(s)	Novartis Europharm Limited
Joint PASS	No
Research question and objectives	With this non-interventional study, real-world data will be gathered on the potential impact of co-administration of a

	HMG-CoA reductase inhibitor (statin) together with LCZ696 with respect to a potentially increased risk of statin-associated toxicity, namely of myotoxicity, hepatotoxicity, and acute pancreatitis
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
MAH contact person	[redacted]

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List of abbreviations

ACE(I)	Angiotensin Converting Enzyme Inhibitor
ADM	Administrative
ALF	Acute Liver Failure
ALI	Acute Liver Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Acute Pancreatitis
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CK	Creatine Kinase
c_{max}	Maximal Plasma Concentration
CPRD	Clinical Practice Research Datalink
CRO	Contract Research Organization
CYP	Cytochrome P450
DDD	Defined Daily Dose
DDI	Drug-Drug Interaction
db	Database
DILI	Drug-induced Liver Injury
DK	Denmark
EMA	European Medicines Agency
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERCP	Endoscopic Retrograde Cholangiopancreatography
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 CSD Longitudinal Patient Database
ICD-9	The International Classification of Diseases, 9th Revision
ICD-10	The International Classification of Diseases, 10th Revision
ICPC	International Classification of Primary Care
IQR	Interquartile Range

IR	Incidence Rate
Ita	Italy
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
MRA	Mineralocorticoid Receptor Antagonist
MC	Medical Center
NIS	Non-Interventional Study
NL	The Netherlands
NHS	National Health Service
NYHA	New York Heart Classification
OATP	Organic Anion-Transporting Polypeptide
OR	Odds Ratio
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
RCT	Randomized Controlled Trial
Rx	Prescription
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
UMLS	Unified Medical Language System
UK	United Kingdom
US	United States
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Responsible parties

Table 1-1 Main responsible parties

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

2 Abstract

Title

Non-interventional post-authorization multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of sacubitril/valsartan (Entresto®)

Version and date

v00 – 29 November 2016

Name and affiliation of main author

[redacted]

Rationale and background

LCZ696 (sacubitril/valsartan; Entresto®) is a novel treatment initially approved in the United States, the Europe Union (EU) and a number of other countries in 2015. In the EU, Entresto® is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Based on the observation that sacubitril inhibits OATP1B1 and OATP1B3 transporters *in vitro* Novartis conducted a drug-drug interaction (DDI) study with atorvastatin (a HMG-CoA reductase inhibitor [statin] in which LCZ696 increased the maximal plasma concentrations (c_{max}) of the OATP1B1 and OATP1B3 substrates atorvastatin and its metabolites by up to 2-fold. However, the areas under the curve (AUCs) of atorvastatin and its metabolites were not increased to a clinically significant extent (<1.3-fold), suggesting that the impact of sacubitril on the pharmacokinetics of atorvastatin is limited to c_{max}. Therefore, the EU SmPC recommends "that caution should be exercised when co-administering Entresto with statins".

To further elucidate the potential of LCZ696 to interact with OATP1B1 and OATP1B3 substrates, Novartis conducted another clinical DDI study – completed after the Entresto® EU submission – using simvastatin. Simvastatin is a prodrug and metabolized to the active metabolite simvastatin acid which is a more sensitive OATP1B1 and OATP1B3 substrate. LCZ696 has no clinically significant impact on exposures of both simvastatin and simvastatin acid when simvastatin was co-administered with LCZ696.

Based on the atorvastatin study, and given the high proportion of patients expected to be on a concomitant statin post-marketing, the Committee for Medicinal Products for Human Use (CHMP) requested that Novartis consider further evaluation of this potential DDI in the post-marketing setting. In the approved Entresto® EU Risk Management Plan (RMP Version 1.4), Novartis therefore committed to perform a (non-imposed) non-interventional post-authorization safety study (PASS, category 3) dedicated to assess specific statin-associated safety events, namely myotoxicity, and hepatotoxicity, in association with concomitant use of statins together with LCZ696 in patients with HF. In addition, in the Pharmacovigilance Risk Assessment Committee (PRAC) RMP Assessment Report from September 2015, Novartis was asked by the PRAC Rapporteur to "consider including pancreatitis to the list of statin-related events".

Research question and objectives

The study will provide real-world data on the potential impact of co-administration of a statin together with LCZ696 to evaluate the potential for an increased risk of myotoxicity, hepatotoxicity or acute pancreatitis.

Study design

The design is a case-control study for each of the three outcomes outlined above (i.e. myotoxicity, hepatotoxicity, and acute pancreatitis) in adult patients using statins and having a recorded diagnosis

of HF with secondary use of electronic healthcare data retrieved from data sources from the Netherlands, the United Kingdom (UK), Spain, Italy, and Denmark.

Population

The study period starts at the launch date of LCZ696 in the countries of interest. Subjects are eligible to be part of the study base if they have at least one year of valid data, are 18 years or older, and have a HF diagnosis as well as recorded statin use at the index date.

Variables

Main exposures are statins and LCZ696, primary outcome measures are myotoxicity, hepatotoxicity and acute pancreatitis. Covariates are drugs that may interact with statin pharmacokinetics, as well as risk factors for the outcomes.

Data sources

Data sources are five European electronic healthcare data sources, i.e. three primary care information databases, one each from Spain (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP]), Italy (Health Search CSD Longitudinal Patient Database [HSD]), and UK (Clinical Practice Research Datalink [CPRD]) and two record linkage databases from the Netherlands (PHARMO Database Network [PHARMO]) and Denmark (Aarhus University Prescription Database [Aarhus]). All data sources are listed as data sources of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

Study size

Forty cases with hepatotoxicity will allow ruling out a 3-fold increased risk assuming a case to control ratio of 1:4 and conservatively, that 20% of the statin-exposed HF patients concomitantly use LCZ696 in the control group. For myotoxicity and acute pancreatitis a total of 19 cases will allow ruling out a 5-fold increased risk.

Data analysis

Main analyses will be based on conditional logistic regression models to estimate the individual relative risks (expressed as odds ratios [ORs]) for the three outcomes of interest during current concomitant use of statins with LCZ696 compared to current use of statins alone. Secondary analyses focus on dose, duration and individual statins.

Milestones

Start of data collection: 30 June 2017

End of data collection: 30 September 2019

Study progress report 1: Q4 2017

Study progress report 2: Q4 2018

Registration in the EU PAS register: After PRAC/CHMP endorsement of the protocol

Final report of study results: 30 June 2020

3 Amendments and updates

Major updates compared to the previous LCZ696B2015 protocol version 0.0 (dated 13-July-2016) include:

- All analyses will be performed in collaboration between [redacted] the scientific lead, and [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
- 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
- For the myotoxicity outcome, a cut-off of 5 x ULN will be used for 'significant increase in CK', and 10 x ULN for severe myopathy (rhabdomyolysis) – see Annex 3 Section 12.3.2.1

4 Milestones

Table 4-1 PASS Study milestones

Milestone	Planned date
Start of data collection	30 June 2017
End of data collection	30 September 2019
Study progress report 1	Q4 2017
Study progress report 2	Q4 2018
Registration in the EU PAS register	After PRAC/CHMP endorsement of the protocol
Final report of study results	30 June 2020

5 Rationale and background

LCZ696 (sacubitril/valsartan [Entresto®]) is a novel therapy approved in adult patients for treatment of symptomatic chronic heart failure (HF) with reduced ejection fraction (HF-rEF).

LCZ696 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 PARADIGM-HF (the 'Prospective Comparison of ARNI [Angiotensin Receptor Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial'), a large pivotal phase III outcome trial in more than 8,400 HF patients with NYHA class II-IV and an ejection fraction ≤40%, LCZ696 significantly reduced the composite endpoint of cardiovascular mortality and the risk of hospitalization. It also significantly decreased the symptoms and physical limitations associated with HF compared with the ACEI enalapril. The LCZ696 group had higher proportions of patients with hypotension and non-serious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group (McMurray et al 2014).

LCZ696 has been approved in 2015 in the United States (US), the European Union (EU), and in various other countries (e.g. Chile, Saudi-Arabia, Switzerland, Kuwait, Taiwan, Argentina, Canada, Israel, Australia, Singapore).

Based on the observation that sacubitril inhibits the organic anion-transporting polypeptides OATP1B1 and OATP1B3 *in vitro* Novartis conducted a drug-drug interaction (DDI) study with the HMG-CoA reductase inhibitor atorvastatin (Pan et al 2013 – CLCZ696B2115 Full Study Report) in which LCZ696 increased the maximal plasma concentrations (c_{max}) of the OATP1B1 and OATP1B3 substrates atorvastatin and its metabolites by up to 2-fold. However, the areas under the curve (AUCs) of atorvastatin and its metabolites were not increased to a clinically significant extent (<1.3-fold), suggesting that the impact of sacubitril on the pharmacokinetics of atorvastatin is limited to c_{max}, potentially due to the short half-life of sacubitril (~1.5 h). Indeed, sacubitril is rapidly absorbed and rapidly metabolized to form LBQ657 and does not result in a DDI with valsartan, another OATP1B1/1B3 substrate. Furthermore, no significant increase in potential statin-related adverse events was observed in PARADIGM-HF, wherein patients were co-administered with LCZ696 200 mg bid and any statin (N=2,369).

Therefore, the EU SmPC recommends "that caution should be exercised when co-administering Entresto with statins".

To further elucidate the potential of LCZ696 to interact with OATP1B1 and OATP1B3 substrates, Novartis conducted a subsequent clinical DDI study – completed after the Entresto® EU submission – using simvastatin (Anon 2015 – LCZ696B2132 Full Study Report). Simvastatin is a prodrug and metabolized to the active metabolite simvastatin acid which is a more sensitive OATP1B1 and OATP1B3 substrate (Niemi et al 2011). No clinically significant DDI was observed between simvastatin and LCZ696 when simvastatin was co-administered with LCZ696.

Based on the atorvastatin study, and given the high proportion of patients expected to be on a concomitant statin treatment post-marketing, CHMP requested that Novartis to consider further evaluation of this potential DDI in the post-marketing setting. In the approved Entresto® EU Risk Management Plan (RMP Version 1.4), Novartis therefore committed to perform a (non-imposed) non-interventional post-authorization safety study (PASS, category 3) dedicated to assess specific statin-associated safety events, namely myotoxicity and hepatotoxicity, in association with concomitant use of statins together with LCZ696 in patients with HF. In addition, in the Pharmacovigilance Risk Assessment Committee (PRAC)

RMP Assessment Report from September 2015, Novartis was asked by the PRAC Rapporteur to "consider including pancreatitis to the list of statin-related events".

Myotoxicity

Statin-induced myotoxicity is a common adverse event (AE) of this drug class and is a significant barrier to maximizing their cardiovascular risk reduction (Sathasivam 2012). The clinical spectrum of statin-induced myotoxicity varies greatly. Myopathy is the general term used to describe all muscle-related adverse events, asymptomatic elevations of creatine kinase (CK) without muscle pain are generally referred to as myalgia, muscle pain or weakness with raised CK levels (typically < 10-times upper limit of normal [ULN]) as myositis, and, finally, as rhabdomyolysis those muscular events with muscle symptoms, high CK (typically > 10-times ULN), and potential for acute kidney injury (Sathasivam 2012, Alfirevic et al 2014). However, the terminology used to describe statin-induced myotoxicity is often imprecise, inconsistent and confusing due to the many definitions used. A useful proposed guide is to break down the clinical spectrum of statin-induced myotoxicity into myalgia, myositis, rhabdomyolysis, and an asymptomatic increase in the concentration of the muscle enzyme CK (Sathasivam 2012).

The underlying mechanisms of statin-induced myotoxicity have not been fully determined; however, several mechanisms have been suggested. These include isoprenoid depletion, decreased sarcolemmal membrane cholesterol, inhibition of ubiquinone or coenzyme Q10 (CoQ10) synthesis, disturbed calcium metabolism or an autoimmune occurrence (Rosenson 2004, Sathasivam 2012, Alfirevic et al 2014). A variety of risk factors for statin-induced myotoxicity have been described (Alfirevic et al 2014, Keen et al 2014) which are included in Annex 3 Section 12.3.1.

The incidence of statin myopathy varies between studies mainly due to the different definitions of myopathy (Tomaszewski et al 2011). In addition, the incidence of myopathies reported in non-interventional studies (NIS) is higher compared to those from randomized clinical trials (RCTs). The reasons for these differences are thought to be due to e.g. the exclusion of patients with risk factors for myotoxicity from RCTs, the strict application of criteria to define myotoxicity, as well as the inclusion of a run-in phase in RCTs, and the failure to systematically document myalgias as most patients in RCTs were not interviewed for mild muscle symptoms (Sathasivam 2012).

Population-based NIS vary considerably with respect to the reported incidence of myopathy which may be highly dependent on the frequency of CK measurement. Van Staa et al (2014) reported that only 20% of patients have a CK measurement recorded in the United Kingdom (UK) based Clinical Practice Research Datalink (CPRD). A study that used data from two different primary care databases in the UK (i.e. 'The Health Improvement Network' [THIN] and 'IMS MediPlus') reported a 10-fold difference in the incidence of myopathy in statin users (Molokhia et al 2008).

In a cohort study using primary care information from the UK, Gaist et al (2001) found an incidence rate (IR) of myopathy in association with current statin use of 1.2/10,000 person-years (PYs). Cziraky et al (2006) reported an IR of 1.6-3.5/10,000 PYs for statin monotherapy-associated myopathy requiring hospitalization (including rhabdomyolysis)

based on US administrative health claims data. McClure et al (2007) estimated – in a cohort of patients with CK monitoring in a managed care organization population from the US – an IR of 9.1/10,000 PYs for myositis in statin-exposed patients without liver or renal disease and without concomitant fibrate exposure and an IR of 639/10,000 PYs in statin-treated patients with liver and renal disease and with concomitant fibrate use. The corresponding IR estimates in a cohort without CK monitoring from the same study was markedly lower (i.e. 2.2 and 593/10,000 PYs, respectively). Molokhia et al (2008) estimated an annual incidence of statin-induced myopathy or myalgia of 6.9/10,000 population based on data from THIN, a UK primary care database. Smeeth et al (2009) report a cumulative incidence for any diagnosed muscle problems of 4.1/10,000 in the first year of statin treatment. Hippisley-Cox and Coupland (2010) estimated an IR for moderate or serious myopathy of approximately 1-2/10,000 PYs in another population-based study in primary care patients from England and Wales. Nichols and Koro (2007) report 'prevalence rates' in statin initiators (without diabetes) of 268/10,000 PYs for any myopathic event, 67/10,000 PYs for myalgia, 45/10,000 PYs for mild myositis (with normal CK), and 8/10,000 PYs for severe myositis (CK 4-10 x upper limit of normal [ULN]).

Population-based NIS reported IR estimates of statin-associated rhabdomyolysis ranging between 0.1 to 2 cases per 10,000 PYs (Graham et al 2004, McAfee et al 2006, Law and Rudnicka 2006, Nichols and Koro 2007, Enger et al 2010, García Rodríguez et al 2010, Cziraky et al 2013, van Staa et al 2014).

Hepatotoxicity

Clinical trials have shown that statin use has been associated with elevations in serum alanine aminotransferase (ALT) levels in approximately 3% of persons who take the drugs. Such elevations are not clinically significant in the great majority of cases; indeed, ALT levels > 3-times ULN are seen in only a small minority of patients and only in the first year of treatment (Beltowski et al 2009). With continued use, the mild elevations of serum aminotransferases generally resolve. This phenomenon, which has been observed for a number of drugs, is not well understood but has been called 'adaptation' (Thapar et al 2013).

Clinically important drug-induced liver injury (DILI) is very rare with statin use. The adaptive response (drug tolerance) possibly helps to prevent statin-induced DILI (Lewis 2012).Patterns of liver abnormalities seen with statins include: (1) asymptomatic elevations of ALT: usually transient and mild (ALT < 3-times ULN), as already described; (2) hepatitis: with ALT > 3-times ULN and clinical symptoms of liver disease; (3) cholestatic or mixed hepatitis: with development of jaundice; and (4) autoantibody-associated DILI with the presence of antinuclear antibody (ANA) and anti-smooth muscle antibody or anti-mitochondrial antibody with or without plasma cells on liver biopsy. Acute liver failure (ALF) develops in a very small minority of persons who are taking statins; indeed, the incidence is not different from that in the general population (Thapar et al 2013). A systematic review of published data from RCTs reported that the incidence of ALT ≥ 3-times ULN (≥ 120 U/L) in statin-treated patients was 30/10,000 PYs (Law and Rudnicka 2006).

A systematic review of the literature published in 2009 however, only identified 40 cases of statin hepatotoxicity, mostly from single case reports and no case series with more than four patients (Russo et al 2009). The 'US Acute Liver Failure Study Group' reported six cases of

ALF attributed to statins among a total 131 cases of acute liver failure due to drugs other than acetaminophen over a 10-year period (Reuben et al 2010). Russo et al (2014) described 22 cases of statin-associated DILI based on information from the 'US Drug Induced Liver Injury Network' (DILIN) registry. The median age was 60 years (range 41-80), and 68% were female. The latency to onset of liver injury ranged from 34 days to 10 years (median = 155 days). Median peak levels were ALT 892 U/L (> 22-times ULN), alkaline phosphatase (ALP) 358 U/L, and total bilirubin 6.1 mg/dL. Nine patients presented with cholestatic hepatitis and 12 patients presented with hepatocellular injury, of which six had an autoimmune phenotype. Nine patients were hospitalized, four developed evidence of hepatic failure, and one died. All commonly used statins were implicated. Based on reports on adverse hepatic reactions suspected to be due to statins submitted to the Swedish Adverse Drug Reactions Advisory Committee between 1988-2010 (including only cases with > 5-times ULN in aminotransferases and/or ALP > 2-times ULN) Björnsson et al (2012) estimated an IR of statin-associated DILI of 1.6/10,000 PYs for statins overall, ranging from 0.5 to 17/10,000 PYs for individual statins.

Published non-interventional cohort studies provide highly varying estimates for hepatotoxicity associated with statins, mainly due to the different definitions used for hepatotoxicity. Chalasani et al (2004) report a 6-month cumulative incidence of 1.9% for mild-moderate transaminase elevations (i.e. AST and/or ALT up to 10 x ULN) and 0.2% for severe elevations (i.e. serum bilirubin > 3 mg/dL [regardless of baseline transaminases] or elevations of AST and/or ALT > 10 x ULN) in statin-exposed patients with normal baseline liver enzymes. Cziraky et al (2006) using US health claims data information reported an IR of hepatic events leading to hospitalization (identified by ICD-9 codes and including acute/subacute necrosis of liver, hepatitis, other specified disorders of the liver, unspecified disorders of liver) for various statins (as monotherapy) ranging from 6.1-12.9/10,000 PYs. Hippisley-Cox and Coupland (2010) reported an IR for moderate or serious liver dysfunction (defined as > 3-times ULN [i.e. > 120 U/L] of ALT among patients without diagnosed chronic liver disease) based on UK data of 15.2 and 17.4/10,000 PYs in women and men, respectively. Enger et al (2010) reported an IR of 0.9/10,000 PYs for hepatic injury requiring hospitalization (identified by ICD-9 codes and including acute/subacute necrosis of liver, hepatic coma, hepatorenal syndrome, hepatitis unspecified, hepatic infarction, other specified disorders of the liver, unspecified disorders of liver) in patients exposed to statins using health claims data information from a US managed care plan. Katz et al (2013) reported that the type of case definition used and the availability of data in observational databases greatly impact on the frequency of cases found, which may explain the variability across databases.

Acute pancreatitis

Several drugs that are frequently used by patients with heart failure (e.g. statins, diuretics, ACE inhibitors [ACEIs]) have been associated with pancreatitis (Jones et al 2015).

Use of statins has been suggested as a possible risk factor for acute pancreatitis (AP) based on a number of case reports, in which statins have been linked with AP (Johnson and Loomis 2006, Singh and Loke 2006, Thisted et al 2006, Etienne and Reda 2014).

However, the evidence on the association between statins and the risk of AP is inconclusive. Various case-control studies have suggested that statins statistically significantly increase the

risk of AP with adjusted odds ratios (ORs) reported ranging from 1.3 to 3.2 (Thisted et al 2006, Lai et al 2015, Kuoppala et al 2015). The risk seemed to be elevated more in the first year of statin use (Kuoppala et al 2015). Contrary to these case-control studies, a recent cohort study with secondary use of database information from Kaiser Permanente Southern California – an integrated healthcare system data from southern California –found that simvastatin use was associated with a substantially decreased risk of pancreatitis (adjusted relative risk 0.29; 95% CI 0.27-0.31). A similarly reduced risk was also found in association with atorvastatin exposure (Wu et al 2015). In another large cohort study, with secondary use of primary care electronic medical record information from the UK, statin exposure was not associated with an altered risk of pancreatitis (Smeeth et al 2009). In addition, a prospective cohort study from Croatia suggested that prior statin treatment significantly reduces morbidity and mortality in AP (Gornik et al 2013). However, these findings could not be reproduced in cohort study with secondary use of data from a tertiary medical center's database in Taiwan (Shiu et al 2015). Finally, in a recent pooled analysis of RCT data based on 16 placebo- and standard care-controlled statin trials with 113,800 participants, use of statin therapy was associated with a lower risk of pancreatitis in patients with normal or mildly elevated triglyceride levels (Preiss et al 2012).

Enger et al (2010) reported an IR of pancreatitis with statins as monotherapy of 4.6/10,000 PYs. The annual incidence of AP not related to alcohol was estimated at 5 per 10,000 adult statin users in Finland (Kuoppala et al 2015). An IR of 29.2/10,000 PYs was reported by Wu et al (2015) in association with use of simvastatin.

Mechanisms for all types of drug-induced pancreatitis have been described by Jones et al (2015) and comprise pancreatic duct constriction, cytotoxic and metabolic effects, accumulation of a toxic metabolite or intermediary, and hypersensitivity reactions. Hypertriglyceridemia and chronic hypercalcemia that may be related to drug use are also mechanisms for drug-induced acute pancreatitis, as these effects are risk factors for acute pancreatitis. Other possible mechanisms of action are localized angioedema effect in the pancreas and arteriolar thrombosis (Jones et al 2015).

The onset of acute pancreatitis induced by statins has been observed from hours to years after treatment. Because of the variance in the latency period, the mechanism may be related to a direct toxic effect to the pancreas and the accumulation of a toxic metabolite. Other mechanisms of action of statin-induced acute pancreatitis are speculated to be associated with rhabdomyolysis, myalgia, and/or metabolism or drug interactions through cytochrome P-450 3A4 (CYP3A4). In several case reports, either myalgia or rhabdomyolysis occurred before development of acute pancreatitis (Jones et al 2015). ACEIs are also risk factors for pancreatitis (Jones et al 2015). A possible mechanism for ACEI-induced acute pancreatitis is proposed to follow the mechanism of local angioedema of the pancreatic duct. ACEIs decrease the degradation of bradykinin that is linked to the development of angioedema. In addition, angiotensin II receptors may be important in regulating secretion and microcirculation within the pancreas (Jones et al 2015).

6 Research question and objectives

The study will provide real-world data on the potential impact of co-administration of a statin together with LCZ696 to evaluate the potential for an increased risk of myotoxicity, hepatotoxicity, or acute pancreatitis.

The study objectives are listed below.

6.1 Primary objective

- To assess the relative risk of myotoxic events associated with concomitant exposure of LCZ696 together with statins compared with statin exposure alone in patients with HF
- To assess the relative risk of hepatotoxic events associated with concomitant exposure of LCZ696 together with statins compared with statin exposure alone in patients with HF
- To assess the relative risk of acute pancreatitis associated with concomitant exposure of LCZ696 together with statins compared with statin exposure alone in patients with HF

7 Research methods

7.1 Study design

This will be a non-interventional, multi-database, post-authorization safety study (PASS) using a case-control design with secondary use of electronic healthcare data. The study will retrieve information from various European electronic healthcare databases, i.e. one each from the UK, the Netherlands (NL), Spain (ES), Italy (IT), and Denmark (DK). See Section 7.4 for details on the data sources to be used for the study.

Cases will be identified from the study base, which are adults, have HF and statin exposure during follow-up, at least one year of valid data (i.e. at least one year of database history available for a patient, meaning the patient was registered in the database for at least one year), and have a safety event of interest (either myotoxicity, hepatotoxicity or acute pancreatitis) during follow-up. Control patients (without a recorded event of interest prior to the index date of the case) will be matched to cases based on age (at index date), sex (see Section 7.2.2.4), and index date (= calendar date). Exposure to LCZ696 and statins in cases and matched controls within a certain risk period prior to the index date (= date of safety event of interest) will be assessed. There will be three separate case-control analyses, one each for myotoxicity, hepatotoxicity, and acute pancreatitis.

A case-control analysis is an effective method to assess potential DDIs on a population-based, real-world level using electronic healthcare information, since we are interested in the relative risk. It is more efficient to assess concomitant drug use at one point in time (i.e. at the index date) over the risk period rather than the entire period of follow-up, especially in this population that uses many different types of drugs. This type of design has been applied many times for assessing various different DDIs on a population-level using electronic healthcare databases (e.g. Cressman et al 2015, Pincus et al 2012, Jobski, Behr and Garbe 2011, Juurlink et al 2011, Schellemann et al 2011, Juurlink et al 2009, Schellemann et al 2008).

7.2 Setting

7.2.1 Source population

The source population for this study will be based on enrollees from five EU electronic healthcare databases, namely the 'Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) from Spain, the 'PHARMO Database Network' (PHARMO) from the Netherlands, the 'Health Search CSD Longitudinal Patient Database' (HSD) from Italy, the 'Aarhus University Prescription Database' from Denmark, and the UK 'Clinical Practice Research Datalink' (CPRD). Additional databases may be added if needed (e.g. from Germany). For details on the databases, see Section 7.4 'Data sources'.

7.2.2 Study population

7.2.2.1 Study base

The study base will be all subjects (≥ 18 years of age) recorded in any of the databases during the study period (see Section 7.2.2.2) with at least one year of valid data and having a recorded HF diagnosis and a statin prescription.

7.2.2.2 Study period

The study period starts at the launch date of LCZ696 in the countries of interest (see (planned) launch dates in Table 7-1 below).

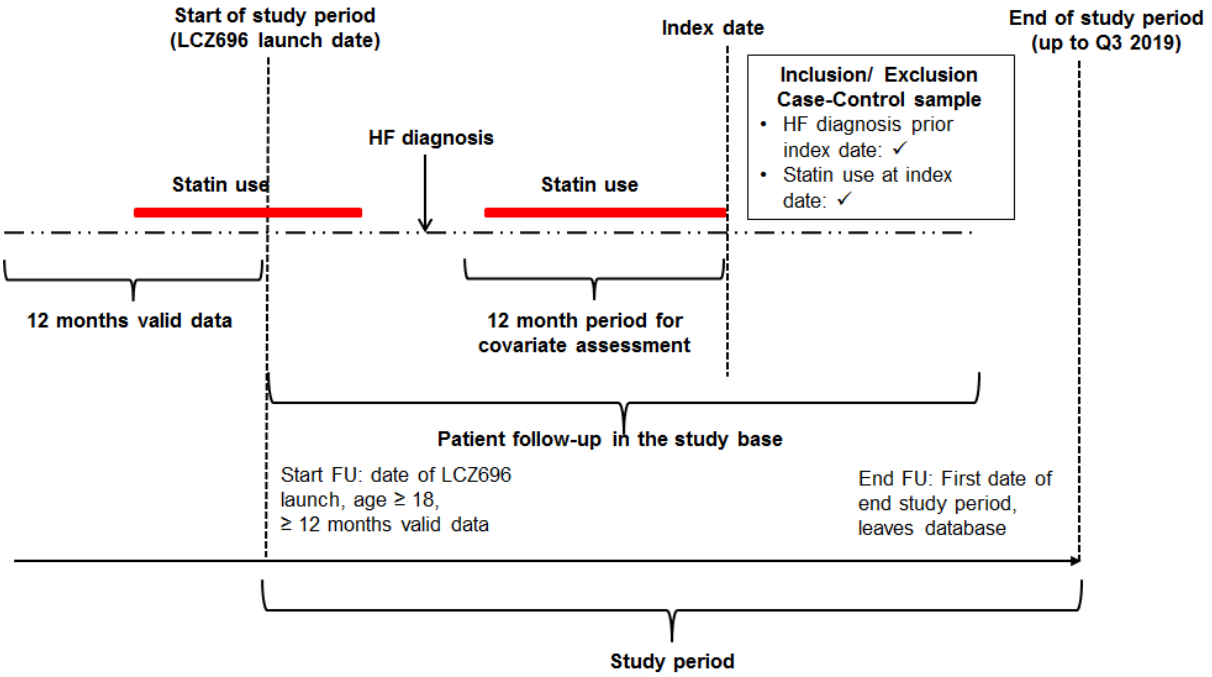
Table 7-1 LCZ696 (Entresto®) launch date in the countries of interest

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

The period over which information is retrieved for each subject may start before the launch date. The study period ends for each reporting at the date that the databases will download their data for the study (see Table 7-5) or when the practices last supplied the data, which will allow for the use of the most updated data.

A graphical display of the design including information on start of study period, follow-up of subjects in the study base and end of study etc. can be found below in Figure 7-1.

Figure 7-1 Graphical display of the study design



FU = follow-up; HF = heart failure

7.2.2.3 Start and end of follow-up

Follow-up for each subject in the study base will start at the latest of the following points in time:

- Start date of LCZ696 launch
- Reaching age 18 years
- Having at least one year of valid data in the database (to allow for assessment of co-morbidities)

Follow-up ends at the earliest of the following dates:

- Last data download in practice
- Date that the patient transfers out of the database
- Date of death

7.2.2.4 Case-control sample

7.2.2.4.1 Inclusion

Within the population base (see above, Section 7.2.2.1), all subjects with a new (first-time) episode of myotoxicity (and separately, all cases of hepatotoxicity, or with acute pancreatitis) that occur during follow-up will be identified (Section 7.2.2.3).

To qualify as a case, patients need to have (i) a HF diagnosis before the event, (ii) have current statin exposure at the index date (= recorded date of the outcome of interest). These

cases will be matched to all potentially available control patients (i.e. study base subjects without the outcome of interest at the index date of the case and still in follow-up) from the same data source and who also have a HF diagnosis together with current statin exposure at the corresponding index date. Controls will be matched to cases on age (year of birth), sex and index date. Controls will have the same calendar date as index date as their matched case.

The incidence density sampling will be done separately for all three outcomes of interest, i.e. separately for myotoxicity, hepatotoxicity, or acute pancreatitis.

7.2.2.4.2 Exclusion

Cases and/or their matched controls who have any of the recorded outcomes of interest will be excluded:

- No recorded heart failure diagnosis at or prior to the index date
- No current or recent use of statins (see Section 7.3.1) at the index date
- History of the particular event of interest prior to the start of follow-up or during follow-up:
  - For myotoxicity, we will exclude subjects with a history of myotoxicity prior to start of follow-up (both in cases and controls)
  - For hepatotoxicity, we will exclude subjects with a hepatotoxic event prior to start of follow-up (chronic, acute, viral, or drug-induced) (both in cases and controls)
  - For the acute pancreatitis outcome, we will exclude subjects with recorded pancreatitis (acute or chronic, or pancreatic cancer) as well as myotoxicity prior to start of follow-up (as myalgia or rhabdomyolysis have been reported before development of acute pancreatitis [Jones et al 2015]) (both in cases and controls)

7.3 Variables

7.3.1 Exposures of interest

Drug exposures of primary interest are statins and LCZ696. Information on these variables will be obtained from the prescription/dispensing files (for codes for statins, see Annex 3 Section 12.3.2, Table 12-1). 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. Exposure to LCZ696 will be assessed at the index date (date of outcome of interest) and categorized in the following categories of recency of use:

- Current use: the prescription duration covers the index date or stops at most 7 days before
- Recent use: exposure ends between 8 and 90 days before the index date

For current users of LCZ696 at the index date, we will further classify the duration of exposure in the following categories:

- Short: Current use and initiated within past 30 days prior to index date
- Middle: Current use and initiated within past 31-90 days prior to index date
- Long: Current use and initiated more than 90 days prior to index date

For current users of statins, we will look at the daily dose in DDD equivalents for the statin component (see Annex 3, Section 12.3.3, Table 12-1) of the most recent prescription and categorize as:

- Low (< 1 DDD)
- Medium (1 DDD-1.5 DDD)
- High (> 1.5 DDD)

For the secondary analyses (see Section 7.7.2.3), the type of statin that is used closest to the index date will determine the type of statin.

Other exposures of interest will be drugs that may confound or modify the potential association; these are listed under the covariates (see Section 7.3.3). All drugs will be extracted on the basis of their 'Anatomical Therapeutic Chemical' (ATC) codes, and durations calculated as described above for the main exposures of interest.

7.3.2 Outcomes of interest

Outcomes of interest will be identified using the event-specific codes based on the coding system(s) used in the database(s) of interest (e.g. READ, International Classification of Diseases, 9th or 10th revision [ICD-9, or ICD-10], International Classification of Primary Care [ICPC]). Laboratory values will in general only be used to verify the certainty of a diagnosis, which may be used in sensitivity analyses (e.g. any case, laboratory confirmed cases only). Cases will not be identified based on using laboratory data alone to avoid inclusion of asymptomatic cases that were coincidentally detected because of screening that happened for other purposes.

Suggested terms that will be included in the mapping are listed in Annex 3 Section 12.3.2. Narrative searches for identification of cases will be limited to PHARMO as free text does not add value or is absent/unavailable in the other databases.

7.3.2.1 Myotoxicity

Myotoxicity is defined as myalgia (muscle pain without evidence of raised CK), myositis (muscle symptoms with raised CK, typically < 10-times ULN), rhabdomyolysis (muscle symptoms with markedly raised CK, typically > 10-times ULN). Since not all of the database may systematically record all CK levels, we will not look at asymptomatic CK increases. These conditions will be identified using event-specific codes and laboratory measurements where available. Based on the publication by Wiley et al (2015), which made a systematic assessment of different phenotyping algorithms using US electronic medical record (EMR) data, the best performance is a combined approach of codes, laboratory measurements and textual searches. However, this may not be possible in all databases or applicable to EU data. Database specific algorithms will be developed. Table 7-2 shows the components that may be used for each of the databases.

For individual terms to identify cases with myotoxicity, see Annex 12.3.2.1.

Validation will be performed for all potential cases in the databases that allow for this and have not yet validated these outcomes before. We will also assess the number of potentially

missed cases that were asymptomatic but had raised CK levels, to assess the potential impact on the study results.

Table 7-2 Components for the identification of myotoxicity by database

	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 (CK)	Yes	Yes	Yes	Yes	Yes
Text / symptoms	Yes	No	No	No	No

CK = creatine kinase; CPRD = Clinical Practice Research Datalink; DK = Denmark; ES = Spain; 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; UK = United Kingdom

Note: details on databases, see Section 7.4

7.3.2.2 Hepatotoxicity

Based on the level of elevation of transaminases or alkaline phosphatase (ALP) and the ratio (R) of elevation of baseline ALT to baseline ALP (ALT/ULN)/(ALP/ULN), drug-induced liver injury (DILI) is classified as either hepatocellular, cholestatic or mixed types (hepatocellular DILI: ALT ≥ 3-times ULN and R ≥5; cholestatic DILI: ALP ≥ 2-times ULN and R ≤ 2; mixed DILI: ALT > 3-times ULN and ALP > 2-times ULN and R > 2-times < 5-times (Benichou 1990, Devarbhavi 2012). Not all the databases will allow for classification of the type of liver injury since ALT and ALP may not be available. Database specific algorithms based on codes, values and natural language processing (NLP) will be developed in line with the work done by Overby et al (2013) in the USA and Afzal et al (2013) in the Netherlands, where they explored various definitions of liver injury in electronic health care databases. Table 7-3 shows the components that may be used for each of the databases. Viral hepatitis will be excluded from the cases.

For individual terms to identify cases with hepatotoxicity, see Annex 3 Section 12.3.2.2.

Validation will be performed for all potential cases in the databases that allow for this and have not yet validated these outcomes.

Table 7-3 Components for the identification of hepatotoxicity by database

	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 (ALT/ALP)	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; ES = Spain; 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; UK = United Kingdom

Note: details on databases, see Section 7.4

7.3.2.3 Acute pancreatitis

Acute pancreatitis is characterized by the onset of parenchymal and peripancreatic fat necrosis with associated inflammation in a previously healthy individual.

Acute pancreatitis describes an acute inflammatory process of the pancreas that rapidly depletes intravascular water and, if unchecked, promotes regional inflammation. Commonly accepted criteria for a clinical diagnosis of acute pancreatitis necessitate the presence of 2 of the 3 following features: serum amylase and lipase elevated at least 3-times ULN; characteristic epigastric abdominal pain; and typical radiologic features as found on computed tomography (CT), magnetic resonance imaging (MRI), or transabdominal ultrasound (US) (Frossard 2008). Acute pancreatitis has been investigated in several European multicenter database studies such as EU-ADR and SAFEGUARD, and the algorithms for identification of acute pancreatitis and the validity will be obtained from these consortia.

Table 7-4 shows the components that may be used for each of the databases.

For individual terms to identify cases with acute pancreatitis, see Annex 3 Section 12.3.2.3.

Validation will be performed for all potential cases in the databases that allow for this and have not yet validated these outcomes.

Table 7-4 Components for the identification of acute pancreatitis by database

	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 (amylase/lipase)	Yes	Yes	Yes	Yes	Yes
Text / symptoms	Yes	No	No	No	No

CPRD = Clinical Practice Research Datalink; DK = Denmark; HSD = Health Search CSD Longitudinal Patient Database; ES = Spain; 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 Covariates

7.3.3.1 General

Co-variates are all variables which are associated with the specific outcome and those that may increase the systemic concentrations of statins. The latter will be assessed for all outcomes at the index date and comprise:

- Concomitant use of drugs potentially interacting with statins at the index date (current use at index date see Section 7.3.1):

  Cytochrome P450 (CYP3A4) enzyme inhibitors (particularly important for the CYP3A4 substrates simvastatin, lovastatin, and atorvastatin), e.g. diltiazem, verapamil, clarithromycin, telithromycin, erythromycin, itraconazole, cyclosporine, protease inhibitors (ritonavir, indinavir, and saquinavir), amiodarone, and fusidic acid

  CYP2C9 enzyme inhibitors (with effects on fluvastatin, a CYP2C9 substrate): e.g. omeprazole, fluconazole

  OATP1B1 inhibition (with effects on atorvastatin, simvastatin, pravastatin, lovastatin, and rosuvastatin): e.g. gemfibrozil

Complete lists for these interacting drugs will be described in the statistical analysis plan (SAP) based on resources from prior studies and relevant open source databases.

In addition, we will look at covariates that will be associated with statin use and proxies for HF severity in all analyses.

- Number of statin prescriptions in the year prior to index date
- Number of different ATC codes in the year prior to index date
- 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
  - Angina pectoris
  - Atrial fibrillation
  - Valvular disease
  - Diabetes mellitus
  - Respiratory disease (asthma, chronic obstructive pulmonary disease [COPD])
- Comedication at 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

7.3.3.2 Covariates for myotoxicity

The presence of the following variables will be assessed at the index date:

- Obesity (in year prior to index date)
- Hypothyroidism (in year prior to index date)
- Hypovitaminosis D (in year prior to index date)
- Chronic renal insufficiency (any time prior to index date)
- Infections (in 90 days prior to index date)
- Liver impairment (in year prior to index date)
- Alcohol abuse (in year prior to index date)
- Surgery (in 90 days prior to index date)
- Metabolic disorders (any time prior to index date)

Codes, drugs and algorithms to identify these covariates will be developed and described in the SAP.

7.3.3.3 Covariates for hepatotoxicity

- Drugs causing acute or cholestatic hepatotoxicity (within 90 days before index date): e.g. isoniazid, pyrazinamide, rifampicin, ibuprofen, nimesulide, cotrimoxazole, phenytoin, dapsone, chlorpromazine, amoxicillin-clavulanic acid, flucloxacillin, carbamazepine, phenytoin, fluoroquinolones, acetaminophen [paracetamol]) (Devarbhavi and Andrade 2014)
- Alcohol abuse (in year prior to index date)
- HIV infection (in year prior to index date)

Codes, drugs and algorithms to identify these covariates will be developed and described in the SAP.

7.3.3.4 Covariates for acute pancreatitis

- Gallbladder disease (gallstones) (in year prior to index date)
- Alcohol abuse (in year prior to index date)
- Hypercalcemia (in year prior to index date)
- Hypertriglyceridemia (in year prior to index date)
- Trauma (90 days prior to index date)
- Endoscopic retrograde cholangiopancreatography (ERCP) (90 days prior to index date)

- Cholecystectomy (90 days prior to index date)
- Drugs associated with acute pancreatitis including ACEIs (90 days prior to index date) (Jones et al 2015)

Codes, drugs and algorithms to identify these covariates will be developed and described in the SAP.

7.4 Data sources

This study will be conducted by using five 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 and will be used through a Novartis license, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) from Spain provided by IDIAP Jordi Gol, the Health Search CSD Longitudinal Patient Database (HSD) from Italy provided by Società Italiana di Medicina Generale, the PHARMO Database Network (PHARMO) from the Netherlands provided by the PHARMO Institute for Drug Outcomes Research, and the Aarhus University Prescription Database from Denmark provided by Aarhus University.

All analyses will be performed in collaboration between [redacted], the scientific lead, and [redacted], the coordinating centre for the study according to contractual agreements.

Table 7-5 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 and PHARMO from the Netherlands) and available data are complete as they come from the general practitioners' [GPs] electronic primary care records. The primary care databases represent 3-20% of the country specific total population. The total number of persons in the source population encompassing all five databases will be around 16 million in 2016.

Table 7-5 Overview of databases to be used for the study

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

Characteristic	PHARMO	CPRD	Database Aarhus	HSD	SIDIAP
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)	Monthly (2-times a year for HES)	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)
Laboratory data	Yes	Yes	yes	Yes	Yes

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; CPRD = Clinical Practice Research Datalink; EMR = Electronic Medical Records; HES = Hospital Episode Statistics; HSD = Health Search CSD Longitudinal Patient Database; ICD= International Classification of Disease, ICPC = International Classification of Primary Care; Rx = prescription; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

* 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 2010, Jick et al 2003).

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

7.4.1 Clinical Practice Research Database (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. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. 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 ICD code), 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 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, prescription and corresponding pharmacy invoicing data, specialist referrals, and primary care laboratory test results. Hospital admissions and their major outcomes can be identified for a number of practices, covering a total 1.7 million active patients. Health professionals gather this information using ICD-10 codes (primary care records) and ICD-9 (hospital admissions), 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 CSD Longitudinal Patient Database (HSD) – Italy

The Italian arm of the study will use the Health Search CSD 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. Laboratory values are available. 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 (PHARMO) – 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

The sample size is calculated following a non-inferiority approach (Wang and Chow 2007), with the intent to demonstrate that the increased risk due to LCZ696 exposure is less than 3-fold for hepatotoxicity and less than 5-fold for myotoxicity or acute pancreatitis.

Forty cases with hepatotoxicity will allow ruling out a 3-fold increased risk with a one-sided test (80% power, 5% type I error), assuming a conservative case:control ratio of 1:4 and conservatively, that 20% of the statin-exposed HF patients concomitantly use LCZ696 in the control group (Table 7-6).

Assuming an incidence rate of acute hepatic events in statin-treated HF patients of 6.1 and 12.9/10,000 PYs (Cziraky et al 2006), the underlying study base is expected to be comprised of at least about 66,000 and 31,000 patient-years (PYs), respectively.

A total of 19 cases with a myotoxic event will allow ruling out a 5-fold increased risk (Table 7-6). Assuming IR of myopathy in statin-treated HF patients between 2.3 and 9/10,000 PYs (Macedo et al 2014), the underlying study base should comprise of at least about 83,000 and 21,000 PYs, respectively.

The underlying study base should comprise of at least about 38,000 PYs in order to observe 19 cases of acute pancreatitis assuming an IR of statin-associated acute pancreatitis of 5/10,000 PYs (Kuoppala et al 2015).

Table 7-6 Sample size scenarios for a one-sided non-inferiority test (80% power, 5% type 1 error)

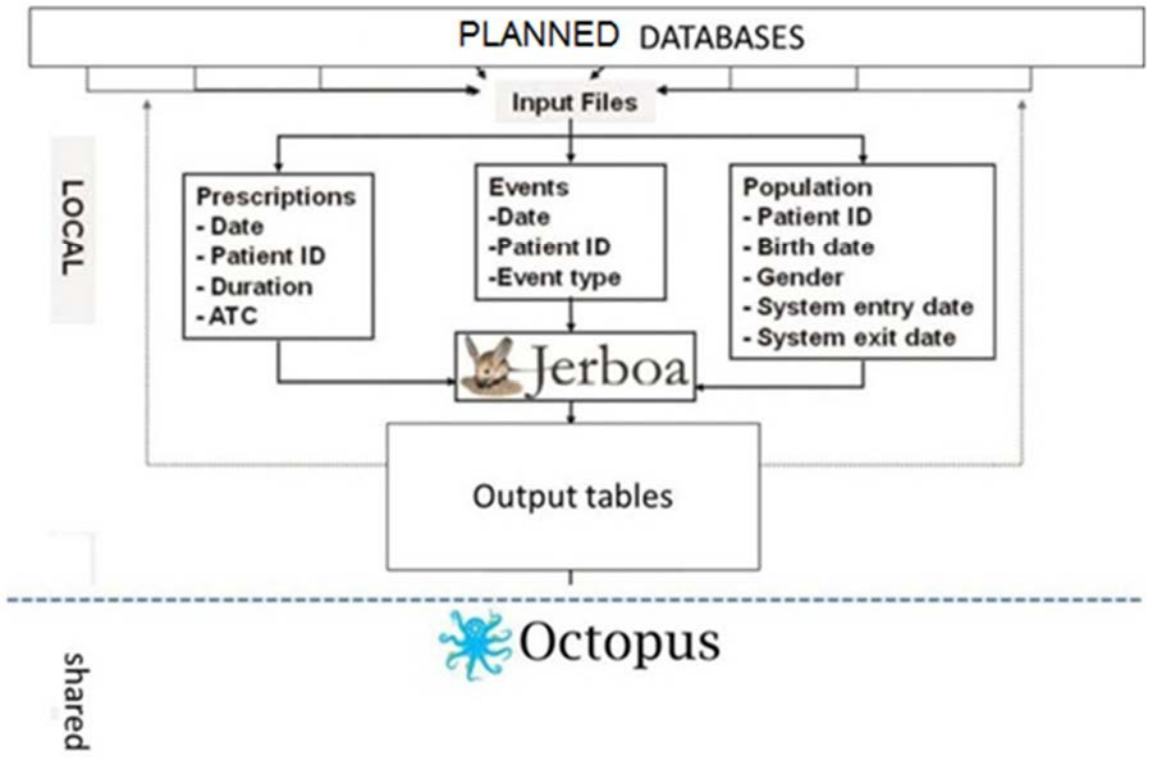
Risk to be ruled out	No of cases needed	
	with 10% LCZ696 use	with 20% LCZ696 use
5	33	19
3	71	40

Risk to be ruled out	No of cases needed	
	with 10% LCZ696 use	with 20% LCZ696 use
2	179	100

7.6 Data management

Data extraction and elaboration is done locally and pooling of aggregated data is done on a remote research environment (see Figure 7-2 for overview).

Figure 7-2 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 and covariates will be ascertained using a list of agreed ICD (UK, Denmark, Italy, Netherlands, and Spain), ICPC (Netherlands) and READ (UK) codes. The proposed lists of codes will be created following a number of steps:

1. Case definition
2. Preliminary list of concept identifiers using codemapper to UMLS Metathesaurus Browser

3. Addition of codes found after literature review of validated lists of codes for each of the study outcomes in each of the databases; and
4. 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.

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.

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 [redacted].

7.6.1 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.

7.6.2 Data sharing

A study-specific folder on the central Octopus remote research environment (RRE) for secure access by members will be used to analyze 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 analyzed. SAS, version 9.4 (SAS Institute Inc., Cary, NC), will be used for post-processing of data.

7.7 Data analysis

All analyses will be performed at the [redacted] the scientific lead for this multi-database study, in close collaboration with [redacted], the coordinating centre for the study . Data will be deposited in the remote research environment and participating partners can inspect the analysis by remotely accessing.

Below the main statistics are described, a detailed SAP will be prepared after PRAC/CHMP endorsement of the protocol.

7.7.1 Analyses timing

Yearly progress reports will be submitted with a first report based on 2016 data to be expected in Q1 2018.

These progress reports will include the following information:

- Size of the study base and exclusions
- Number and % of LCZ696 users
- Number of cases for each of the primary outcomes of interest

7.7.2 Final analysis

The final analysis based on validated cases will be conducted at the end of the study (after reaching the necessary number of cases) and is expected to be submitted in Q2 2020.

7.7.2.1 Attrition diagram

Reasons for exclusion of cases and controls will be described with a detailed attrition diagram.

7.7.2.2 Demographic and baseline characteristics

Demographic and clinical characteristics of case and control patients at the index date of the case-control analysis will be described separately for each outcome of interest using contingency tables for categorical variables and mean, standard deviation (sd), range, median and interquartile range (IQR) for continuous variables in each individual database.

7.7.2.3 Primary and secondary analyses

Conditional logistic regression analyses will be used to estimate crude and adjusted relative risks (expressed as odds ratios [ORs]) of each specific outcome with corresponding 95% confidence intervals (CIs).

The primary analysis is current LCZ696 and statin versus current use of statin (any dose) without current use of LCZ696.

Secondary analyses comprise investigation of dose of statin and duration of LZC696, recent use of LZC696 or statins, and individual statins. In the dose specific analysis for statins the reference category will be current low dose of statins and non-use of LCZ696.

7.7.2.4 Confounding

Control for confounding will be based on matching and matched analyses plus adjustments based on the change in estimate method as proposed by Maldonado and Greenland (1993) per database.

7.7.2.5 Sensitivity analyses

Sensitivity analyses that focus on the limitations will be conducted and described in the SAP, this comprises evaluation of the effect of missing first prescriptions of LCZ696.

7.7.2.6 Handling of missing values/censoring/discontinuations

No imputations will be done.

7.7.2.7 Pooling

All estimates will be calculated by database and pooled. The adjusted odds ratios estimated with the logistic regression model in each database will be combined in a two-stage meta-analysis using a fixed-effects model and a random-effects model employing the DerSimonian- and Laird method (DerSimonian and Laird 1986). Given the poor performance of the significance tests for statistical heterogeneity no such testing will be used. Rather, the estimates will be presented as outcomes of the fixed and random effects model respectively. In addition, to optimize power, we will conduct a one-stage model, that will estimate the effects putting all individual level data together while accounting for the matching of cases and controls. One-stage meta-regression may also be used to investigate the sources of heterogeneity and adjust for structural differences between the data sources when appropriate.

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 the statistical analyses.

7.9 Limitations of the research methods

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 and alcohol use; or body mass index [BMI] which is a very dynamic variable and which is not well recorded or not recorded at all) are contained in (all) databases, this may lead to residual confounding.

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 some misclassification of exposure, however, we do capture recency of exposure and can explore the effects of dose in PHARMO and CPRD which will allow us to assess the extent of this effect. Since LCZ696 may be prescribed by specialists initially we may misclassify exposure if it is not recorded in the databases. This would attenuate an effect since it is likely to be non-differential; a sensitivity analysis will be planned to address this.

All of the databases, apart from the Aarhus University Prescription Database and PHARMO, have information on prescription only and not on dispensing. None has information on actual drug intake. This implies that we do not know whether the patient actually took the drug – however, this may be non-differential leading to underestimation of risk.

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. Laboratory measurements will be needed for case finding/validation and the availability of these data will vary across the databases. The amount of misclassification of the outcome may differ between databases due to differences in availability of validation data or laboratory confirmations. However, since cases and controls are sampled and analyzed within the same database, misclassification will be similar for matched cases and controls in the same database. Bias due to misclassification of the outcomes may just differ between the databases.

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 to the patient's care. In addition, specialist information is incomplete in the majority of the databases. Aarhus and PHARMO contain all reimbursed prescriptions from GPs and specialists. The other databases are primary care databases, so they may not capture all prescriptions of specialists. However, in all of these countries (UK, Italy, and Spain), the GP is the gatekeeper of care and prescriptions initiated by the specialist are continued by the GP. Missing information on LCZ696 exposure may lead to some misclassification of duration in the secondary analyses.

None of the databases will be able to capture over-the-counter (OTC) drug use. This may be relevant for instant with respect to use of acetaminophen in the context of hepatotoxicity, as most acetaminophen use will be OTC and prescription use will be limited.

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 "up-to-date data" at study end.

The most important uncertainty is about the uptake of LCZ696, which may limit the power of the study.

7.10 Other aspects

Not applicable.

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 anonymized 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 an y 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 governance boards 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 study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety

relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and an outcome. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

9.1 Other aspects

Not applicable.

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 as well as the RECORD statement. The study will be registered in the ENCePP /EU-PAS registry.

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 assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of sacubitril/valsartan (Entresto®)

Study reference number:

LCZ696B2015

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

Comments:

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				

[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)**
an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	12-17
2.1.2 The objective(s) of the study?	☒	☐	☐	18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	18-21
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
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	22-24
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)	☒	☐	☐	35

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	18, 19
4.2 Is the planned study population defined in terms of:				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.1 Study time period?	☒	☐	☐	19
4.2.2 Age and sex?	☒	☐	☐	19
4.2.3 Country of origin?	☒	☐	☐	19
4.2.4 Disease/indication?	☒	☐	☐	19
4.2.5 Co-morbidity?	☒	☐	☐	25
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	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)	☒	☐	☐	21-22
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)	☒	☐	☐	36
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	21
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?	☒	☐	☐	21, 22

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?	☒	☐	☐	22-24
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)	☐	☐	☐	22-24, 33, 34, 36, 37

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	24-26, 35
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	22

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.)	☒	☐	☐	27-31
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.)	☒	☐	☐	27-31
8.1.3 Covariates?	☒	☐	☐	27-31
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,				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
dose, number of days of supply prescription, daily dosage, prescriber)				
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	27-31
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	27-31
	☒	☐	☐	27-31
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	27-31
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	27-31
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	27-31
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	27-31

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	32

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?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
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?	☒	☐	☐	35, 35
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	33-34
11.3 Are methods of quality assurance described?	☒	☐	☐	34, 36
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	27-31, 36-38
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	22-24, 36
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)	☒	☐	☐	36
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up	☐	☐	☐	36

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
in a cohort study, patient recruitment)				
12.3 Does the protocol address other limitations?	☒	☐	☐	35-36

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?	☒	☐	☐	37, 38
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	37, 38

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?	☒	☐	☐	12

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)?	☒	☐	☐	38, 39
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	38, 39

Comments:

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

Date: / /

Signature: _____

12.3 Annex 3 – Additional information

12.3.1 Risk factors for statin-induced myotoxicity

A variety of risk factors for statin-induced myotoxicity have been described (Alfirevic et al 2014, Keen et al 2014):

- Advanced age (> 80 years of age)
- Female sex
- Low body mass index (BMI)
- Comorbidities (e.g. hypothyroidism, hypovitaminosis D, chronic renal insufficiency [especially when associated with diabetes], infections, liver impairment, hypertension, alcohol abuse)
- Physical exercise
- Surgery
- Personal/family history of statin myopathy
- Underlying metabolic conditions (carnitine palmitoyltransferase II deficiency, myophosphorylase deficiency, CoQ10 deficiency, myoadenylate deaminase deficiency)
- Higher statin dose
- Concomitant use of interacting drugs

  Cytochrome P450 (CYP3A4) enzyme inhibitors (particularly important for the CYP3A4 substrates simvastatin, lovastatin, and atorvastatin: e.g. diltiazem, verapamil, clarithromycin, telithromycin, erythromycin, itraconazole, cyclosporine, protease inhibitors (ritonavir, indinavir, and saquinavir), amiodarone, and fusidic acid

  CYP2C9 enzyme inhibitors (with effects on fluvastatin, a CYP2C9 substrate): e.g. omeprazole, fluconazole

  OATP1B1 inhibition (with effects on simvastatin, pravastatin, lovastatin, and rosuvastatin): gemfibrozil
- Diet-related interactions (e.g. grapefruit juice)

12.3.2 Terms for outcome mapping

12.3.2.1 Myotoxicity

Rhabdomyolysis, Muscle necrosis, Myoglobinaemia, Myopathy, Myositis, Necrotising myositis, Myalgia

CK > 5-times ULN for ‘significant increase in CK’

CK > 10-times ULN for severe myopathy (rhabdomyolysis)

12.3.2.2 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

12.3.2.3 Pancreatitis

Pancreatitis, Acute pancreatitis, Pancreatic haemorrhage, Pancreatic necrosis

12.3.3 Statins – ATC codes and defined daily dose (DDD)

Table 12-1 ATC codes and defined daily dose (DDD) for statins (including fixed-dose combinations

ATC code	Substance	DDD (mg)
C10AA01	simvastatin	30
C10AA02	lovastatin	45
C10AA03	pravastatin	30
C10AA04	fluvastatin	60
C10AA05	atorvastatin	20
C10AA07	rosuvastatin	10
C10AA08	pitavastatin	2
C10BX01	simvastatin and acetylsalicylic acid	
C10BX02	pravastatin and acetylsalicylic acid	
C10BX03	atorvastatin and amlodipine	
C10BX04	simvastatin, acetylsalicylic acid and ramipril	
C10BX05	rosuvastatin and acetylsalicylic acid	
C10BX06	atorvastatin, acetylsalicylic acid and ramipril	
C10BX07	rosuvastatin, amlodipine and lisinopril	
C10BX08	atorvastatin and acetylsalicylic acid	
C10BX09	rosuvastatin and amlodipine	
C10BA01	lovastatin and nicotinic acid	
C10BA02	simvastatin and ezetimibe	
C10BA03	pravastatin and fenofibrate	
C10BA04	simvastatin and fenofibrate	
C10BA05	atorvastatin and ezetimibe	
C10BA06	rosuvastatin and ezetimibe	
A10BH51	sitagliptin and simvastatin	

ATC = Anatomical Therapeutic Chemical; DDD = defined daily dose