PASS Information

Title	SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments
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Joint PASS	No
Research question and objectives	This study research question of interest is to evaluate the long-term cardiovascular safety of lisdexamfetamine (LDX) in adults. To address this research question, the study will include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with LDX use.
Country(-ies) of study	Denmark and Sweden
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Approval Page: RTI Health Solutions

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Authors	Cristina Rebordosa, MD, PhD (RTI Health Solutions)
Version	3.0

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Version	3.0

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2 List of Abbreviations

ADHD	attention deficit hyperactivity disorder
AMI	acute myocardial infarction
ATC	Anatomical Therapeutic Chemical (classification system)
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPRD	Clinical Practice Research Datalink
DDD	defined daily dose
ECG	electrocardiogram
EMA	European Medicines Agency
EMACE	extended MACE endpoint
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union electronic register of postauthorisation studies
HR	hazard ratio
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
ICD-10-CM	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*
ICD-8	*International Classification of Diseases, 8th Revision*
ICD-9	*International Classification of Diseases, 9th Revision*
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IR	incidence rate
IRR	incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
LDX	lisdexamfetamine dimesylate
MACE	major adverse cardiovascular events
MI	myocardial infarction
PASS	postauthorisation safety study
PBRER	periodic benefit-risk evaluation report
PPV	positive predictive value
Q*n*	quarter of a calendar year
RTI-HS	RTI Health Solutions
SAP	statistical analysis plan
SCD	sudden cardiac death
SD	standard deviation
SVA	serious ventricular arrhythmia
TIA	transient ischaemic attack
US	United States
WHO	World Health Organization

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4 Abstract

Title: SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Users of Other ADHD Treatments

Version 3.0, 15 March 2019

Cristina Rebordosa, MD, PhD, RTI Health Solutions, Epidemiology

Rationale and background: Lisdexamfetamine dimesylate (LDX) received marketing authorisation approval for the treatment of attention deficit hyperactivity disorder (ADHD) in adults in several European countries, including Denmark and Sweden. As part of the marketing authorisation approval, Shire was asked to examine the long-term safety of LDX in adults using surrogate markers for the potential risks of cerebrovascular disorders and ischaemic cardiac events.

Research question and objectives: This study will address the following research question of interest: what is the long-term cardiovascular safety of LDX in adults? To address this research question, the study will include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with LDX use.

The primary objective of this study is to estimate, in real-world settings, the incidence rate (IR) and the adjusted incidence rate ratios (IRRs) of the composite major adverse cardiovascular events (MACE) endpoint in a cohort of adult patients who are current new users of LDX (the LDX cohort) compared with a cohort of remote users of other ADHD treatments in two European data sources. Combined IRs and IRRs for all data sources will also be estimated, as appropriate.

The secondary objectives are as follows: (1) to evaluate the potential long-term effects of LDX use by estimating the IR and IRRs of MACE among long-term LDX users (i.e., current LDX users with ≥ 12 months of cumulative duration of current LDX use) compared with long-term remote users of other ADHD treatments without exposure to these treatments for a period of at least 12 months after the start of follow-up; (2) to estimate the IR and IRR of all secondary endpoints—an extended MACE endpoint (EMACE) comprising all MACE components plus hospitalisation for either unstable angina or transient ischaemic attack (TIA), the composite coronary and stroke components of EMACE, and a composite of sudden cardiac death (SCD) and serious ventricular arrhythmias (SVAs)—comparing current LDX use versus remote use of other ADHD treatments; and (3) to estimate the IR and IRR of MACE by subcategories of concomitant use of other ADHD medications during current LDX use ("current single LDX use" and "current multiple drug use", i.e., LDX plus one or more other ADHD drugs), compared with remote use of other ADHD treatments.

Additional exploratory analysis will estimate the IR and IRR of MACE for LDX users versus those of remote users of other ADHD treatments, by subcategories of current LDX dose, stratified by sex and age categories and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions. Also, additional sensitivity analyses will analyse the impact of study eligibility criteria, previous exposure, exposure time, outcome categories, and the unmeasured confounding.

Study design: This study will consist of multiple observational (non-interventional) population-based cohort substudies of patients initiating LDX compared with patients with remote use of other ADHD medications, in two data sources. The frequency of MACE and the adjusted IRRs will be calculated.

The study will compare adult patients who are new users of LDX (the LDX cohort) with a cohort of patients with remote use of other ADHD medications, matched on age, sex, region, and index date. The study will estimate the IR and IRRs with the corresponding 95% confidence interval (CI), for the comparison between the LDX cohort and the remote use of other ADHD treatments cohort. The analysis will be conducted separately in each data source, and overall estimates of effect will be obtained using meta-analytic techniques as appropriate.

Population: A non-interventional population-based cohort study will be conducted using selected electronically available health care data sources: the Danish national registries and the Swedish national registers.

To be eligible for inclusion into the study population, individuals must be adults (aged 18 years or older) and have at least 12 months of data available prior to the index date. The LDX cohort will be formed by adult patients who have a first dispensing for LDX (index date), and no evidence of prior use of LDX in the data source.

The remote use of other ADHD treatments cohort will be generated by selecting adult patients with at least one dispensing for a medication indicated for ADHD, other than LDX, during the 24 months before the index date and with no dispensings of these medications in the 180 days before the index date. The index date of each patient in the remote use of other ADHD treatments cohort will be the index date of the matched LDX new user, which will be at least 181 days after the last ADHD medication dispensing date. These cohort members will be matched in a ratio of up to 5 to 1 to members of the LDX cohort by age, sex, region, and index date.

Variables: The primary endpoint, MACE, will comprise the first occurrence of any of its individual components during follow-up: hospitalisation for acute myocardial infarction (AMI), fatal or non-fatal; hospitalisation for stroke, fatal or non-fatal; out-of-hospital coronary heart disease death; and out-of-hospital cerebrovascular death. Secondary endpoints are an EMACE endpoint that includes hospitalisation for either unstable angina or TIA, the composite coronary and stroke components of EMACE, and an additional secondary endpoint that will be a composite of SCD and SVAs.

Current use for LDX new users is defined as the duration of the LDX dispensing plus 30 days. For the primary analysis, follow-up will end at the earliest of death, first occurrence of an outcome of interest, termination of enrolment in the health plan system, or end of study period. Each patient can have multiple outcomes.

The study will define other variables that will be used to describe the study population and to control for confounding, including history of cardiovascular diseases and hypertension, demographic variables, other medical history, and use of other medications.

Data sources: To obtain sufficient study size and person-years of LDX use to address the objective, the study will be implemented in health care data sources from Denmark and Sweden. In Denmark, the national registries and databases of interest to this study are the Danish Civil Registration System, Danish National Patient Register, Danish Psychiatric Research Central Register, Danish National Prescription Registry, and the Causes of Death Register. In Sweden, the Swedish national databases of interest to this study are the Swedish National Patient Register, Swedish National Prescribed Drug Register, and Swedish Causes of Death Register.

Study size: An LDX cohort size of 7,800 person-years of time at risk of current LDX use should be sufficient to reach, with 80% probability, an IRR upper bound of the 95% CI for the composite MACE endpoint in LDX new users cohort versus remote use of other ADHD treatments cohort of less than 3 (null hypothesis), under the alternative hypothesis that the IRR is 1 and the IR in the remote use of other ADHD treatments cohort is 1 per 1,000 person-years.

Data analysis: Each research partner will conduct country-specific analyses within each data source to (1) select the study population; (2) describe the study cohorts, including patterns of demographics, medical history, exposures, and endpoints; (3) within its data, estimate exposure propensity scores that will be used to control for confounding; and (4) create a summary of aggregated data set based on counts of patients, person-years, and outcome events according to the strata of age, sex and propensity scores. No person-level data will be shared with the coordinating centre.

Using propensity score–stratified tables with aggregated data from each database research partner, the coordinating centre will conduct an analysis of the data from each individual database and an overall analysis combining the data across all databases, as appropriate. Data source-specific and pooled analysis activities will include estimation of crude and adjusted IRs as well as analysis of crude and adjusted IRRs using Poisson regression models.

Milestones:

- Start of data collection: Q3-Q4, 2019
- End of data collection: Q3, 2020
- Annual study progress reports, initially including monitoring counts of adult LDX users (feasibility assessment)
- Final study report: Q4, 2020

5 Amendments and Updates

Protocol revision 3.0 reflects the amendment of the study protocol by removing the analysis in the United Kingdom Clinical Practice Research Datalink (CPRD) in all sections of the protocol following review by the Swedish Medical Products Agency The removal of CPRD from the study is supported by the observed low uptake of Elvanse Adult® in the CPRD. Other updates have been added, including the study team members, the data sources features, exposure and study endpoints definitions, additional sensitivity analyses, update of the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) Checklist for Study Protocols (version 4.0), and update of the study codes in Annex 4.

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
3.0	3 June 2019	PASS Information; Marketing authorisation holder(s); Approval Page: Shire Pharmaceuticals; Section 3, Responsible Parties	Administrative changes	To update responsible parties
3.0	3 June 2019	Sections 4, Abstract; 6, Milestones and Timelines; 7 Rationale and Background; and Section 9, Research Methods; Annex 3, Validity of Endpoint Definitions	The CPRD data source was removed from the study. Removed references to "prescription"	The CPRD database was removed due to the low number of users and low number of events expected. Danish and Swedish data sources use dispensing information; thus, with the removal of the CPRD data source, reference to "prescription" is no longer needed
3.0	3 June 2019	Section 9.2.2, Study Period	The time lag in the Swedish Cause of Death Register has been corrected to 1 year, and the end of study period in Denmark and Sweden has been also corrected	Corrected to most updated information
3.0	3 June 2019	Section 9.3.1, Exposure Assessment	If dexmethylphenidate (ATC code: N06BA11) users are captured in Denmark and Sweden, they will be treated as users of methylphenidate, although no users are expected	This decision was based on the similarities between the two drugs
3.0	3 June 2019	Section 9.3.1.1, Time at Risk for the LDX Cohort	Information on how to treat exposure time from overlapping LDX dispensings has been added	To update the definition on the exposure

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
3.0	3 June 2019	Section 9.3.2.1, Endpoint Identification	ICD-10-CM codes H34.1 and R96.0 have been added to the list of included codes for the study endpoints in Table 2	To update the study endpoint definitions
3.0	3 June 2019	Section 9.3.2.3, Endpoint Validation	This section has been removed	The endpoint validation was only planned in the CPRD. Validation studies of the study endpoints have shown that identification of the cardiovascular outcomes of interest is quite reliable in the planned data sources
3.0	3 June 2019	Section 9.3.3, Other Variables	Two demographics variables have been added: employment and years of education	To be consistent with what is reported by the Danish and Swedish Research Partners at Aarhus University and Karolinska Institutet, respectively
3.0	3 June 2019	Section 9.4, Data Sources	A correction has been made regarding the data on medications in Denmark (data on reimbursed and unreimbursed medications are available since 1995 instead of 1994)	To be consistent with what is reported by the Danish Research Partner at Aarhus University
3.0	3 June 2019	Section 4, Abstract; and Section 9.7.2 Pooled Analysis	Text has been added to indicate that Poisson methods will be used to adjust crude IRs and IRRs instead of standardisation methods	To account for marginal zeros due to the expected low number of events

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
3.0	3 June 2019	Section 9.7.2, Pooled Analysis	Text has been added to indicate that a random-effects Poisson model will be used to pool the adjusted IRs and IRRs obtained in Denmark and Sweden	To account for the small numbers expected
3.0	3 June 2019	Section 9.7.3, Sensitivity Analysis	Two sensitivity analyses have been added	To account for the differences in study inclusion criteria between the LDX cohort and the remote users' cohort and to account for previous exposure to ADHD drugs in the LDX cohort
3.0	3 June 2019	Annex 2, ENCePP Checklist for Study Protocols	Update	To update to version 4.0
3.0	3 June 2019	Annex 4, ICD-10 Codes and ICD-10 Terms for Study Endpoints	Update study codes	To harmonise with the codes proposed in Section 9.3.2

ADHD = attention deficit hyperactivity disorder; ATC = Anatomical Therapeutic Chemical Classification System; CPRD = Clinical Practice Research Datalink; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ICD-10 = *International Classification of Diseases, 10th Revision*; ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; IR = incidence rate; IRR = incidence rate ratio; LDX = lisdexamfetamine dimesylate.

6 Milestones and Timeline

Milestone	Anticipated Date
Registration in the EU PAS Register	Q3-Q4, 2016
Study progress report(s)[a]	Annually starting in 2016
Start of data collection[b]	Q3-Q4, 2019
End of data collection[c]	Q3, 2020
Interim report(s)	None planned
Final report of study results	Q4, 2020

EU PAS Register = European Union electronic register of postauthorisation studies; Qn = quarter of a calendar year.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by

approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

[a] Reports will include information on the study progress, and initially a feasibility assessment that includes findings from monitoring the counts of medication users. During monitoring, patient counts will be obtained from publicly available data sources in Denmark and Sweden, Medstats.dk in Denmark (The Danish Health Data Authority, 2015) and the Swedish drug database (Socialstyrelsen, 2014).

[b] Start of data collection is "in the case of secondary use of data, the date from which data extraction starts". (EMA, 2013, Section VIII.B.2).

[c] End of data collection is "the date from which the analytical data set is completely available" (EMA, 2013, Section VIII.B.2).

7 Rationale and Background

Elvanse Adult® (lisdexamfetamine dimesylate [LDX]) has been granted marketing authorisation approval through the European Decentralised Procedure for the treatment of attention deficit hyperactivity disorder (ADHD) in adults in several European countries, including Denmark and Sweden. As part of the marketing authorisation approval, Shire was asked to examine the long-term safety of LDX in adults using surrogate markers for the potential risks of cerebrovascular disorders and ischaemic cardiac events.

This document describes the core protocol for conducting a European, multinational cohort study to assess the risk of major cardiovascular events in adult new users of lisdexamfetamine and in the population with prior but not current use of other ADHD medication. The study will evaluate populations covered in two automated health databases, one each in Denmark and Sweden.

LDX is a therapeutically inactive amphetamine prodrug. Elvanse Adult® is indicated as part of a comprehensive treatment programme for ADHD in adult patients, including first-line pharmacotherapy treatment with LDX.

There has been a concern that stimulants used to treat ADHD may be associated with adverse cardiovascular outcomes, and this potential association has been investigated in population-based non-interventional studies (Schelleman et al., 2013; Westover and Halm, 2012). Among adults, studies evaluating the effect of ADHD treatments on the risk of cardiovascular outcomes showed mixed findings, and although some of the studies reported an association with one of the adverse cardiovascular outcomes under evaluation, uncontrolled confounding and selection bias were primary concerns in these studies. Holick et al. (2009), in a secondary analysis of the United States (US) Ingenix Research Data Mart (2003-2006), found an increased risk (hazard ratio [HR], 3.44; 95% confidence interval [CI], 1.13-10.60) of transient ischaemic attack (TIA) but not cerebrovascular accident (HR, 0.71; 95% CI, 0.34-1.47) among users of atomoxetine or ADHD stimulant medication compared with the general population. However, in this secondary analysis, the authors used an intention-to-treat approach and did not match the cohorts by propensity score as they did in their primary analysis, where they found no association (Holick et al., 2009). Similarly, although Schelleman et al. (2012), in an analysis of US Medicaid (1999-2003) and Health Core Integrated Research Database (2001-2006) reported an increased risk of sudden death or ventricular arrhythmia (HR,

2.74; 95% CI, 2.02-3.71) among users of methylphenidate compared with the general population, the association was attenuated once propensity scores were used to control for confounding (HR, 1.84; 95% CI, 1.33-2.55). In addition, there were inverse associations between high doses of methylphenidate and several outcomes, which according to the authors did not support a causal relationship and were potentially due to lower dosages being prescribed to the patients at higher risk of death (Schelleman et al., 2012). In the same setting and time period, Schelleman et al. (2013) repeated the previous study but with amphetamines and atomoxetine as the exposures of interest and did not find an association with elevated risk of cardiovascular events (Schelleman et al., 2013). Finally, Habel et al. (2011), in a study of more than 440,000 adults from four US study populations (1986-2005), did not find an increased risk of cardiovascular events among individuals exposed to ADHD medications compared with the general population. On the contrary, results suggested that longer exposure duration was protective, although this was reported as "biologically implausible". An alternative hypothesis is that susceptible patients are more likely to experience an event early after starting a causative agent (Habel et al., 2011).

8 Research Question and Objectives

This study will address the following research question:

- What is the long-term cardiovascular safety of LDX in adults?

To address this research question, the study will include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with LDX use, and with long-term LDX use. The study will also include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with concomitant use of other ADHD medication, and an extended definition of the endpoints of interest.

8.1 Primary Objective

The primary objective of this study is to estimate, in real-world settings, the incidence rate (IR) and the adjusted incidence rate ratios (IRRs) of the composite major adverse cardiovascular events (MACE) endpoint in a cohort of adult patients who are current new users of LDX (the LDX cohort) as compared with a cohort of remote users of other ADHD treatments in two European data sources. Combined IRs and IRRs for all data sources will also be estimated, as appropriate.

8.2 Secondary Objectives

- To evaluate the potential long-term effects of LDX use by estimating the IR and the IRRs of MACE among long-term LDX users (i.e., current LDX users with ≥ 12 months of cumulative exposure to LDX, that is those with ≥ 12 months duration of current LDX use) compared with long-term remote users of other ADHD treatments without exposure to these treatments for a period of at least 12 months after the start of follow-up.

- To estimate the IR and IRRs of all secondary endpoints—(1) an extended MACE (EMACE) endpoint comprising all MACE components plus hospitalisation for either unstable angina or TIA, (2) the composite coronary components of EMACE, (3) the composite stroke components of EMACE, and (4) a composite endpoint of sudden cardiac death (SCD) and serious ventricular arrhythmia (SVA)—comparing current LDX use versus remote use of other ADHD treatments, in each data source, and estimating a combined IRR for all data sources, as appropriate.
- To estimate the IR and IRR of MACE by subcategories of concomitant use of other ADHD medications during current LDX use ("current single LDX use" and "current multiple drug use", i.e., LDX plus one or more other ADHD drugs), compared with remote use of other ADHD treatments.

8.3 Specific Aims

This study aims to include sufficient person-time of LDX time at risk to have the upper bound of the 95% CI of the IRR for the composite MACE endpoint in LDX new users cohort versus remote use of other ADHD treatments cohort be less than 3.0 if the true IRR is 1.0. This approach is consistent with the aim to conduct surveillance for a large excess in the rate of specific rare or very rare events with a very low background IR for which there has been no signal from clinical development.

9 Research Methods

9.1 Study Design

9.1.1 Study Tasks

The study will be conducted as a collaborative study involving three research centres: RTI Health Solutions (RTI-HS), which will serve as the coordinating centre, and two database research partners—Aarhus University in Denmark and Karolinska Institutet in Sweden, which will lead the analyses in their respective country databases. Study conduct and coordination will be performed independently from the study sponsor, although responsibility for scientific integrity is shared by the collaborating institutions, including the study sponsor. Each participating database research partner will adapt this core protocol to the specific attributes of the local database.

Responsibilities

The coordinating centre will have the following primary roles and responsibilities:

- Coordinate study activities
- Lead preparation of the final version of this core study protocol with input from all research partners

- Guide database-specific adaptation of the protocol, with a focus on consistency with the core protocol of variable definitions and other methodological aspects across adapted protocols
- Prepare the data on annual monitoring of adult LDX users to be reported by Shire in the periodic benefit-risk evaluation report (PBRER) after being reviewed by research partners
- Provide scientific support to the study implementation phase, including apply for ethics committee approvals, generate a common statistical analysis plan (SAP) and support adapted versions of the SAP for each data source, and develop case validation efforts when needed
- Support the integration of study results by analysing stratified aggregated data from each database research partner to estimate overall IRs and to perform a meta-analysis of the overall measures of effect
- Facilitate research network communications, study reporting, and dissemination of study results

The database research partners will have the following primary roles and responsibilities:

- Provide input into the final version of this core protocol
- Develop the protocol adaptation to each database
- Review data on annual monitoring of adult LDX users to be reported by Shire in the PBRER
- Implement the study in the respective database, including applying for ethics committee approvals, implementing the SAP
- Liaise with the coordinating centre during study implementation as needed
- Contribute to the preparation of study reports and dissemination of results

Shire will have the following primary roles and responsibilities:

- Serve as the study sponsor
- Provide input into the final version of this core protocol
- Review and provide input during the study implementation phase

Sequence of Study Tasks

Because of uncertainties surrounding availability of sufficient numbers of LDX new users to conduct the study, the study will be conducted in phases, initially monitoring annually the number of adult LDX users, and generating a final study report:

- Study progress reports will be produced annually starting in 2016. These study progress reports will include information on the study progress, such as ongoing activities; next steps; and status of the contracts with research partners, adapted protocol, SAP and adapted SAPs, data analyses, and the study results report. At least initially, progress reports will also include results of monitoring counts of LDX users (i.e., during the feasibility phase) until the target sample size is reached.

  - Monitoring the number of adult LDX new users: The accumulating number of LDX new adult users in the data sources will be monitored annually, starting with the number of LDX new adult users during 2016. Data on patient counts will be retrieved from publicly available data sources in Denmark and Sweden, Medstats.dk in Denmark (The Danish Health Data Authority, 2015) and the Swedish drug database (Socialstyrelsen, 2014). The number of adult LDX users will be reported to Shire for inclusion in the PBRER after being reviewed by and in agreement with the study investigators.

- Final study report: This report will include the evaluation of long-term cardiovascular safety of LDX in adults. Collaborating research centres will conduct data source–specific analyses, and the coordinating centre will coordinate and pool the number of events and person-time and conduct the combined analysis, as appropriate.

9.1.2 Research Design

A non-interventional population-based cohort study will be conducted using selected electronic health care data sources: the Danish national registries and the Swedish national registers. The study period in each data source will begin on the date of first recorded dispensing for LDX among adults in each country (2013), including use before the adult indication was granted, and will end with the most recent data available in each data source as of late 2019.

The study will compare adult patients who are new users of LDX (“LDX cohort”) with a cohort of patients with remote use of other ADHD medications, matched on age, sex, region, and index date. The study will estimate the crude and propensity score–standardised IR and the crude and adjusted IRR (with the corresponding 95% CIs) for the comparison between the LDX cohort and the remote use of other ADHD treatments cohort. The analysis will be conducted separately in each data source, and overall estimates of effect will be obtained using meta-analytic techniques as appropriate.

The main composite cardiovascular endpoint of interest, MACE, will comprise the first occurrence of any hospitalisation for fatal or non-fatal acute myocardial infarction (AMI) or for fatal or non-fatal stroke or out-of-hospital coronary or cerebrovascular death. Secondary endpoints will include an extended MACE (EMACE) including additional hospitalisation for either unstable angina or TIA. The composite coronary and stroke components of EMACE will be also evaluated separately, if numbers allow. An additional secondary endpoint will be a composite of SCD and SVA.

This common study protocol will be adapted to the specifications of each of the participating data sources.

9.1.3 Rationale for Choice of Study Design

Population-based health care data sources, which include information from usual health care utilisation, have been used for several decades to evaluate the frequency and risk factors of outcomes among users of medications of interest compared with users of other medications. This population-based approach to evaluating the medication of interest by including diverse countries, practices, and patients is useful for obtaining large numbers of patients, desired precision of outcome frequencies, and broad understanding of the safety profile in diverse types of patients in general health care systems.

A cohort design will allow direct estimation of the absolute IRs and IRRs of multiple outcomes of interest among new users of LDX compared with remote users of other ADHD treatments. A cohort study design will also allow accurate chronological confounder assessment and assessment of the outcomes at multiple time points. The covariate information will be assessed during the time preceding treatment initiation and will include all historical information available for each patient. Follow-up will start the day after treatment initiation.

A case-crossover study design (a type of self-controlled design) was considered not appropriate to address the study objectives because the effect of long-term exposure to LDX was of special interest. In addition, the case-crossover design can be implemented successfully only for an appropriate study hypothesis. Specifically, the exposure must vary over time within a substantial proportion of the study subjects. Because of the self-matching feature, all the elementary comparisons are made within a person; if the exposure remains constant within a person, then there is no information from that person about the possible effect of exposure. The exposure must also have a short induction period and a transient effect; otherwise, exposures in the distant past could be the cause of a recent disease onset. The disease must also have an abrupt onset (Rothman, 2012a; Rothman et al., 2008).

Remote users of other ADHD medications will be selected as the comparator cohort to minimise potential confounding due to the healthy user effect among patients with treated ADHD (Habel et al., 2011). The selection of the comparator cohort was based on the need to select an unexposed comparison group, since an association with cardiovascular events has also been suggested for most of the ADHD drugs in some but not all studies (most commonly stimulants: other amphetamines or methylphenidate) (see Section 7). In addition, the suggested mechanism by which these stimulant drugs would increase the risk of cardiovascular events, an increase in the heart rate and blood pressure (Stiefel and Besag, 2010), would be the same for LDX. A comparison group of patients with ADHD was thought to be less prone to selection bias and confounding by indication than the general population. In addition, since we are evaluating adults, it may be that patients with ADHD are diagnosed and treated during childhood but may not have a recent record of a diagnosis of ADHD during adulthood (Biederman et al., 2010). Thus, by selecting patients with relatively recent use of ADHD drugs (6 to 24 months prior to study entry), we expect to have an adult patient population with ADHD more similar to the LDX cohort than if we selected persons from the general population or untreated patients with an ADHD diagnosis.

Methods to reduce the bias of effect estimates derived from observational studies focus on minimising the differences in the study groups being compared in the absence of randomisation. To control for confounding, exposure propensity scores will be estimated and analyses will be performed by stratifying study patients by ranges of the propensity score. Propensity scores will incorporate measured potential predictors of therapy and outcome as independent variables and exposure group status as the outcome. Because exposure propensity scores focus on the indication for use and non-use of medications, they can be useful to control for confounding by indication. Propensity scores can perform better than conventional regression methods when the number of events relative to the number of potential confounders is small, because rather than having to model the events with many variables, one can instead model the exposure, which may have ample data to accommodate a rich model (Cepeda et al., 2003). This advantage may be important in this study, given the low number of expected events for the study endpoints.

9.2 Setting

9.2.1 Population

The source population will be all individuals aged 18 years or older registered in the study databases from the date LDX will become available for the treatment of ADHD in adults in each country until the end of study period. To be eligible for inclusion into the study population, individuals should have at least 12 months of data available prior to cohort entry. The study will include two cohorts identified from all eligible individuals in the study data sources: the LDX cohort and the remote use of other ADHD treatments cohort.

The LDX cohort will be formed from adults with a dispensing for LDX, at least 12 months of data in the data source before the first dispensing date (index date), and no evidence of prior use of LDX in the data source. The first dispensing of LDX will be the index dispensing, dispensed on the index date during the study period.

The remote use of other ADHD treatments cohort will be generated by selecting adult patients with at least one dispensing for a medication indicated for ADHD, other than LDX, during the 24 months before the index date and with no dispensings of these medications in at least the last 180 days before the index date. The index date of each patient in the remote use of other ADHD treatments cohort will be the index date of the matched LDX new user, which will be at least the 181 days after the last ADHD medication dispensing date. The members of the remote use of other ADHD treatments cohort will be matched to each LDX new user in a ratio of up to 5 to 1 by age, sex, region, and index date. Patients in the remote use of other ADHD treatments cohort will be suitable to be matched from the time point when there has been no dispensing in the previous 180 days for any ADHD medication, after their last dispensing. Patients in the remote users of other ADHD treatments cohort will be matched to LDX new users by applying greedy matching techniques within each category.

The specific inclusion criteria for the LDX cohort are as follows:

- Be aged 18 years or older on the index date
- Have at least 12 months of data available before the index date (patients must not have immigrated during the last 12 months)
- Have no record of prior dispensing of LDX at any time before the index date

The specific inclusion criteria for the cohort of patients with remote use of at least one dispensing for a medication indicated for ADHD, other than LDX, are as follows:

- Be aged 18 years or older on the index date
- Have at least 12 months of data available before the index date (patients must not have immigrated during the last 12 months)
- Have no record of prior dispensing of other ADHD treatments within the last 180 days before the index date but have at least one dispensing between 181 days and 24 months prior to the index date.

Patients from the remote use of other ADHD treatments cohort who initiate LDX will be allowed to enter the LDX cohort if they fulfil the inclusion criteria at the index date.

9.2.2 Study Period

All adult use of LDX will be included, including use before the Elvanse Adult® indication was granted. The study period is defined in each data source as the time between the date of first recorded dispensing for LDX among adults and the latest date of data availability (see Table 1). Data availability in each data source depends on the frequency with which data are updated at each data source and on the approval time necessary for obtaining the data (12 to 24 months in Denmark and 12 to 24 months in Sweden). However, the Danish Register of Causes of Death has a 2-year lag time for data availability. Thus, a 1-year lag time in Sweden and a 2-year lag time in Denmark between the end of the study observational period (December 2017 for Denmark and December 2018 for Sweden) and the submission date of the final study report (late 2020) is needed to obtain cause-of-death data from these two countries.

Table 1. Estimated Study Period in Each Study Data Source

Event	National Registries, Denmark	National Registers, Sweden
LDX initial launch in country[a]	Mar 2013	Sep 2013
Elvanse Adult® approval in Denmark, and Sweden[a]	2015	2015
Study period in each data source (based on first recorded dispensing of LDX in each country among adults and data availability in each data source)[b]	Mar 2013 – Dec 2017	Sep 2013 – Dec 2018

LDX = lisdexamfetamine dimesylate.

[a] Provided by Shire.

[b] All use of LDX among adults is of interest, including data among adults before Elvanse Adult® authorisation was granted.

9.2.3 Follow-up

Follow-up will start at the index date and end on the earliest of the following possible follow-up termination dates for both exposure groups: (1) first diagnosis of any of the individual cardiovascular events of interest for the composite endpoints (an individual can have more than one endpoint and, depending on which composite endpoint is being considered, follow-up may be censored at the first or at a later event date), (2) end of the study period, (3) termination of enrolment in the health plan or system (or emigration), (4) death, or (5) the date a patient in the remote use of other ADHD treatments cohort is prescribed any other ADHD drug.

If a patient in the remote use of other ADHD treatments cohort is prescribed/dispensed LDX he/she will enter the LDX cohort, if all other inclusion and exclusion criteria are met at that date, and his/her time in the remote use of other ADHD treatments cohort will be censored.

9.3 Variables

9.3.1 Exposure Assessment

The **index medication** in the LDX cohort is the lisdexamfetamine (Anatomical Therapeutic Chemical [ATC] code, N06AB12) exposure that qualifies the patient to enter the study. The index LDX dispensing is the first LDX dispensing in the data source delineating entry into the LDX study cohort and initiation of patient follow-up. The index date for the LDX cohort is the date of the index LDX dispensing.

LDX **days' supply** will be estimated similarly in all data sources and will be based on the dispensing information as recorded in each database. When days' supply is not directly provided, this information will be estimated from other information, such as the amount prescribed/dispensed and the defined daily dose (DDD) or numeric daily dose (dosing instructions), the number of individual product packs prescribed, and the pack type or size. The World Health Organization (WHO) definition of a DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO Collaborating Centre for Drug Statistics Methodology, 2009). The DDD for lisdexamfetamine is 30 mg (WHO Collaborating Centre for Drug Statistics Methodology, 2013).

Dose (mg/day) of LDX will be the dose at the index date. When the dose is missing, an attempt to estimate the dose will be made using the available recorded information (e.g., strength, number of units, amount of drug prescribed/dispensed). Information on the amount dispensed (package size and number) and strength is recorded in the Nordic pharmacy-dispensed prescription registries.

The **number of LDX dispensings** will be the total number of repeated dispensings of LDX over the study period.

The **index medication in the remote use of other ADHD treatments cohort** is the last dispensing of other ADHD medications in the data source that occurred at least 180 days before the index date. As previously described, the index date of each patient in the remote use of other ADHD treatments cohort will be the index date of the matched LDX new user, which will be at least 181 days after the last ADHD medication dispensing date. The number and proportion of users of "other ADHD treatments" who qualified for remote use cohort entry by each specific drug substance will be described.

The selection of centrally acting sympathomimetics to be included in the remote use of other ADHD treatments cohort is based on the ATC classification system code N06BA. The following specific ADHD medications will be considered as "other ADHD treatments":

- Amfetamine (ATC: N06BA01)
- Dexamfetamine (ATC: N06BA02)
- Methylphenidate (ATC: N06BA04)
- Atomoxetine (ATC: N06BA09)

No users of dexmethylphenidate (ATC code: N06BA11) are expected to be found in the patient population, but if such users are found, they will be treated as users of methylphenidate. Dexmethylphenidate is available in Sweden. In Denmark, dexmethylphenidate is not listed in the publicly available database (http://medstat.dk/). Other medications included in the same ATC group (N06BA), such as pemoline or modafinil, will not be included in the remote user cohort because their use is very low or absent in the two countries of interest or the main indication is not ADHD.

9.3.1.1 Time at Risk for the LDX Cohort

The time in the denominator of an IR should include every moment during which a person followed is at risk for an event that could get included in the numerator of the rate (Rothman, 2012a). In this study, we are evaluating the IRs and IRRs of cardiovascular events during "current LDX use", which is defined as exposure to LDX plus 30 days after the end of the last dispensing. We postulate that the duration of the effect of LDX exposure starts the same date that the treatment is started and may last up to 30 days after last day of treatment, and this is the reason why a 30-day carryover period has been added to the time at risk for current LDX use. To evaluate whether LDX may have a delayed effect on the risk of cardiovascular endpoints, we will also evaluate whether there is a risk during the time after LDX exposure, which we will call time of "post-LDX use".

Current LDX use will be the sum of periods of continuous LDX use (with dispensing gaps of 30 days or less). Periods of continuous use will be defined as the time elapsed between the date of LDX dispensing start and 30 days after the date of end of days' supply. A gap will be the period between the date of end of days' supply and the date of the next LDX dispensing. After a treatment gap of more than 30 days, follow-up time from the current LDX use category will resume upon LDX re-initiation if a follow-up termination event has not occurred. Exposure time from overlapping dispensings of LDX will be stacked or stockpiled for consecutive dispensings of the same strength (i.e., the start of the subsequent overlapping dispensing will be reassigned to the day after the end of days' supply for the prior dispensing).

Discontinuation of LDX use occurs when there is no repeated dispensing within 30 days after the estimated end of the last dispensing of index medication. Use of another ADHD medication does not affect the estimated time of LDX discontinuation.

Current LDX use will also be classified in subcategories based on duration of current LDX use during follow-up. The patients will accrue person-time in each category in a time-dependent manner: the time at risk in the category of long-term duration will start after 12 months of current LDX use. A cohort member can contribute to person-time in more than one category of duration of current LDX use.

Current LDX use will also be classified in two subcategories based on concomitant ADHD drug use during follow-up:

- "Current single LDX use": time of current use in which the patient is exposed to LDX, and no other ADHD treatments are prescribed/dispensed.
- "Current LDX use, multiple drug use": time of current use in which the patient is exposed to LDX and to at least one other ADHD treatment (i.e., amfetamine, dexamfetamine, methylphenidate, and atomoxetine; see ATC code list in Section 9.3.1).

The primary and secondary analyses will be based on current LDX overall use (i.e., LDX alone or concurrently with another ADHD medication) and duration of LDX use.

Exploratory analyses will estimate the IR and IRRs of MACE by subcategories of LDX dose during current LDX use, compared with remote use of other ADHD treatments.

To account for possible non-adherence, as well as potential persistence of the drug effect after discontinuation, a sensitivity analysis will be performed with an extended carryover period, and the allowed gap between dispensings (30 days in the primary analysis) will be extended to 60 days.

Post-LDX use will be the sum of all periods of time starting after the end of current LDX use and ending at the end of follow-up.

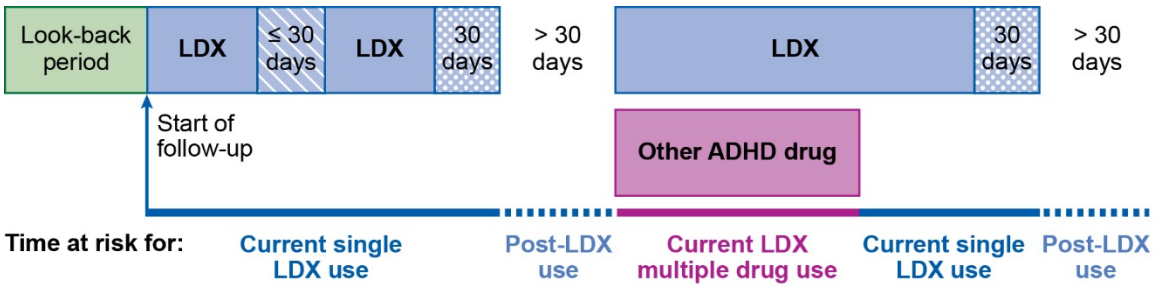
Post-LDX use will be subclassified in two subcategories based on use of "other ADHD treatments" (i.e., amfetamine, dexamfetamine, methylphenidate, and atomoxetine; see ATC code list in Section 9.3.1) during follow-up:

- "Post-LDX use, no ADHD drug use": time of post-LDX use in which the patient is not exposed to any ADHD drug
- "Post-LDX use, with other ADHD drug use": time of post-LDX use in which the patient is exposed to "other ADHD treatment(s)"; exposure to other ADHD treatments during this time may be single drug use or use of multiple drugs at the same time.

During the time of post-LDX use, patients could become current LDX users again if they are dispensed LDX. To evaluate whether there is a delayed or long-term cardiovascular effect of LDX exposure, a sensitivity analysis will be performed comparing post-LDX use versus remote use of other ADHD treatments. To evaluate potential effect of exposure to "other ADHD treatments" in the comparison between post-LDX use versus remote LDX use, an additional secondary analysis will be performed using the time at risk for "post-LDX use, no other ADHD drug use" and "post-LDX use, with other ADHD drug use."

Figure 1 summarises the time periods of patient observation, including those for calculating time at risk from current LDX use of a study medication.

Figure 1. Summary of the Time Periods of Observation for Each Patient in the LDX Cohort



ADHD = attention deficit hyperactivity disorder; LDX = lisdexamfetamine dimesylate.

9.3.1.2 Time at Risk for the Remote Use of Other ADHD Treatments Cohort

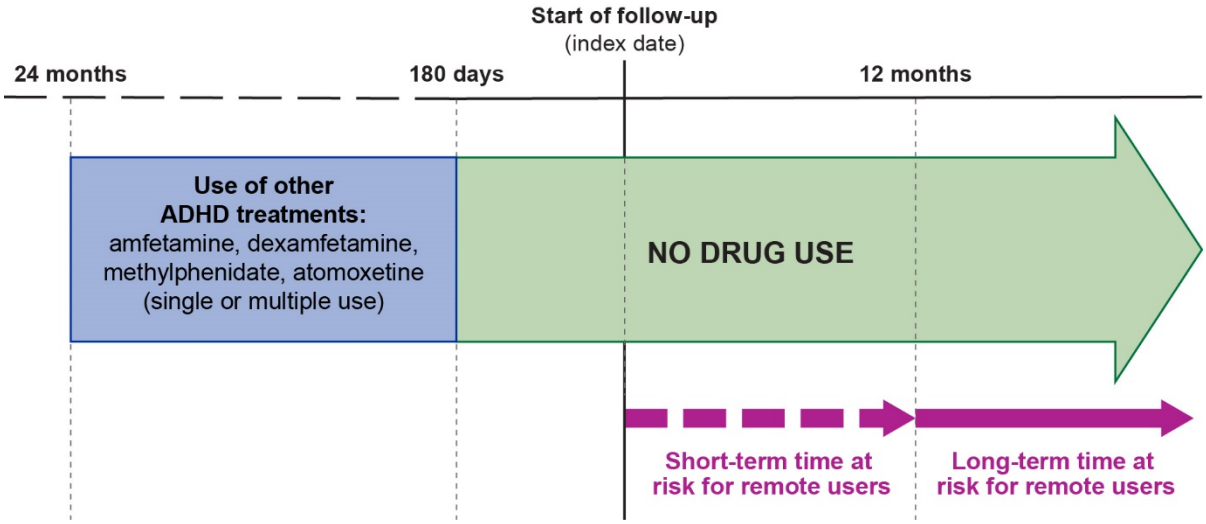
As previously described, the remote use of other ADHD treatments cohort will be generated by selecting adult patients with at least one dispensing for amfetamine,

dexamfetamine, methylphenidate, or atomoxetine during the 24 months before the index date and with no dispensing of these medications in at least the last 180 days before the index date. Thus, follow-up for the remote use of other ADHD treatments cohort will start at the index date (assigned as the index date of the matched pair or index member of the LDX cohort, which will be at least 181 days after the last ADHD medication dispensing date) and end at the end of follow-up (see Figure 2).

If individuals in the remote use of other ADHD treatments cohort start treatment with LDX, their time of follow-up in the remote use cohort will end the day before the LDX dispensing, and they will be allowed to enter the LDX cohort, if all other inclusion criteria for this cohort are fulfilled at that date. If individuals in the remote use of other ADHD treatments cohort start treatment with ADHD drugs other than LDX, their follow-up will end (as described in Section 9.2.3).

Remote users of other ADHD treatments will be classified in subcategories based on duration of follow-up after index date. The patients will accrue person-time in each category in a time-dependent manner: the time at risk in the category of long-term duration of remote use will start after 12 months of follow-up after index date (long-term remote users). A cohort member can contribute to person-time in more than one category of duration of remote use.

Figure 2. Summary of the Time Periods of Observation for Each Patient in the Remote Use of Other ADHD Treatments Cohort



ADHD = attention deficit hyperactivity disorder.

Note: Follow-up for the remote use of other ADHD treatments cohort starts at the index date. Once the follow-up starts, patients in the remote use of other ADHD treatments cohort accrue time in the "short-term remote use" category, and on day 366 after the index date, the patients in the remote use of other ADHD treatments cohort start accruing time in the "long-term remote use" category.

9.3.2 Study Endpoints

The primary endpoint or main composite cardiovascular endpoint of interest, a MACE type, will include the first occurrence of any of the following individual components during the follow-up:

- Hospitalisation for AMI, fatal or non-fatal
- Hospitalisation for stroke, fatal or non-fatal
- Out-of-hospital coronary heart disease death, including SCD
- Out-of-hospital cerebrovascular death

The secondary endpoints of interest are as follows:

1. An expanded composite cardiovascular endpoint, “EMACE”, that includes the first occurrence of any of the following individual components during the follow-up:
    a. Hospitalisation for AMI, fatal or non-fatal
    b. Hospitalisation for unstable angina, fatal or non-fatal
    c. Out-of-hospital coronary heart disease death (including SCD)
    d. Hospitalisation for stroke, fatal or non-fatal
    e. Hospitalisation for TIA, fatal or non-fatal
    f. Out-of-hospital cerebrovascular death
2. A composite “coronary heart disease” endpoint that includes the first occurrence of either a, b, or c, listed in item 1
3. A composite “cerebrovascular” endpoint that includes the first occurrence of either d, e, or f, listed in item 1
4. A composite endpoint that includes SCD and SVA, including ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

Clinical Definitions

The American Heart Association and the World Heart Federation define an AMI by the evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, including ST elevation myocardial infarction (MI) and non–ST elevation MI (Thygesen et al., 2012).

Central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischaemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. Central nervous system infarction occurs over a clinical spectrum; ischaemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms, while silent infarction by definition causes no known symptoms. Stroke also broadly includes intracerebral haemorrhage and subarachnoid haemorrhage (Sacco et al., 2013).

Unstable angina is defined as new cardiac symptoms or a changing symptom pattern with positive electrocardiogram (ECG) findings, a positive stress test, or a relevant ischaemic substrate on coronary angiography, with or without subsequent percutaneous coronary intervention (Luepker et al., 2003).

Transient ischaemic attack is defined by the American Stroke Association as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction (Easton et al., 2009).

Serious ventricular arrhythmias will include torsade de pointes, ventricular flutter, and ventricular fibrillation. Torsade de pointes is characterised by ventricular tachycardia associated with a long QT or QTc interval, and electrocardiographically characterised by twisting of the peaks of the QRS complexes around isoelectric line during the arrhythmia (Zipes et al., 2006).

Sudden cardiac death is defined as a sudden pulseless condition (arrest) that was immediately fatal (or rarely resuscitated with death in 48 hours) and was consistent with a ventricular tachyarrhythmia occurring in the absence of a known non-cardiac condition as the proximate cause of the death (Chung et al., 2010).

Operationally, out-of-hospital coronary heart disease, including SCD, or cerebrovascular death include those who died from a cardiovascular or cerebrovascular cause before reaching the hospital and those who die within 30 days after a hospitalisation for a cardiovascular or cerebrovascular cause.

For assessment of the composite endpoints, only the first of any of the individual components occurring during follow-up will be included. For the assessment of each individual endpoint, only the first event of that specific endpoint occurring during follow-up will be included and the occurrence of one event will not preclude the assessment of a different event type that may happen later. Patients with a prior history of the events of interest will not be excluded at cohort entry, and the presence of prior history of cardiovascular or cerebrovascular events will be taken into account when adjusting the analysis.

9.3.2.1 Endpoint Identification

Events will be identified through (1) hospital discharge diagnoses and (2) cause-of-death records from the cause-of-death registries. To identify events of interest during follow-up, each data source will be searched for electronic codes that indicate potential occurrences of endpoints. A case-finding algorithm in which cases are identified based on a combination of relevant codes for diagnoses, procedures, and pharmaceutical treatments will be customised and implemented in each data source. These algorithms are based on information from prior published and validated case ascertainment algorithms to maximise case ascertainment sensitivity while retaining those with a high positive predictive value (PPV).

The table below presents descriptions of the algorithms for case finding of each endpoint and includes the International Statistical Classification of Diseases and Related Health

Problems, 10th Revision (ICD-10) codes for identification of each outcome. Additional details on the validity of the identification algorithms can be found in Annex 3.

Case Identification

- **Hospitalisation for AMI, stroke, unstable angina, and TIA** events will be identified based on the presence of a hospitalisation with a primary or secondary hospital discharge code (ICD-10) for AMI, stroke, unstable angina or TIA (see Table 2). These events will be considered fatal if the patient died within 30 days after the admission or event date, irrespective of the cause and place of death.
- **Out-of-hospital coronary heart disease death (including SCD) and out-of-hospital cerebrovascular death** events include death events from a cardiovascular or cerebrovascular cause before reaching the hospital. These events will be identified through any out-of-hospital death record with an underlying cause of death recorded in the death certificate being any of the ICD-10 codes listed in Table 2, in the absence of a code for a terminal illness or end-of-life care. The out-of-hospital death endpoint will also include death events that occur outside a hospital setting but within 30 days after a hospitalisation for a cardiovascular or cerebrovascular and that will be identified through a record of out-of-hospital death occurring outside a hospital setting within 30 days after a hospitalisation (admission or event date) for AMI or unstable angina/stroke or TIA, irrespective of the cause of death.
- **SCD / SVA** events will be identified based on the presence of a hospitalisation with a primary or secondary discharge code for SCD or SVA (see Table 2), with SVA either associated or not associated with death at discharge. SCD/SVA events will also include any out-of-hospital death with an underlying cause of death in the death register with any of the listed codes for SCD, SVA, or included in the identification of the out-of-hospital coronary heart disease death and in absence of a terminal illness or end-of-life care. These codes have proved to have high PPV when evaluating SCD and SVA (De Bruin et al., 2005; Johannes et al., 2010; Varas-Lorenzo et al., 2009).

Details on the algorithms and operational definitions will be provided in the SAP.

Table 2. Case Finding of Each Endpoint

Case Finding: ICD-10 Hospital Discharge Codes	
Hospitalisation for AMI	**Hospitalisation for Stroke**
Joensen et al. (2009); Pajunen et al. (2005)	Andrade et al. (2012); Flynn et al. (2010); Kirkman et al. (2009); Kokotailo and Hill (2005); Krarup et al. (2007); Roumie et al. (2008)
▪ I21, Acute myocardial infarction	▪ I60, Subarachnoid haemorrhage ▪ I61, Intracerebral haemorrhage ▪ I63, Cerebral infarction ▪ I64, Stroke, not specified as haemorrhage or infarction ▪ H34.1, Central retinal artery occlusion
Hospitalisation for unstable angina	**Hospitalisation for TIA**
Joensen et al. (2009)	Johnsen et al. (2002)
▪ I20.0, Unstable angina	▪ G45, Transient cerebral ischaemic attacks and related syndromes
Hospitalisation for SVA/SCD	
De Bruin et al. (2005); Johannes et al. (2010); Varas-Lorenzo et al. (2009); Chung et al. (2010)	
▪ I47.0, I47.2, I49.0 ▪ I46.0, I46.1, I46.9 ▪ R96.0, R96.1, R98	
Coronary and cerebrovascular deaths out-of-hospital	
AMI/coronary heart disease death, including SCD	Stroke/cerebrovascular deaths
Chung et al. (2010)	Muller-Nordhorn et al. (2008)
I10, I11.9, I20-I25, I42.8-I42.9, I46, I47.0-I47.2, I49.0, I49.8-I49.9, I51.6, I51.9, I70.9, R96.0, R96.1, R98	I60-I69, G45, H34.1, R96.0, R96.1, R98

AMI = acute myocardial infarction; ICD-10 = *International Classification of Diseases and Related Health Problems, 10th Revision*; SCD = sudden cardiac death; SVA = serious ventricular arrhythmia; TIA = transient ischaemic attack.

Note: When a fourth digit is not specified for an ICD-10 code, all subcategories of that code are included. See the complete list of ICD-10 codes and terms for study endpoints in Annex 4.

9.3.2.2 Case Ascertainment

Each data source will be searched for electronic codes that indicate the possibility of an endpoint of interest using electronic case-finding algorithms.

- Hospitalised cases will be ascertained through primary and secondary hospital discharge diagnoses and considered confirmed if the primary hospital discharge diagnosis code is consistent with one of the codes listed in Table 2 for the corresponding event of interest. Hospitalised cases ascertained through secondary discharge diagnosis codes will not be considered confirmed unless they have gone through a validation process.

- All deaths occurring during the study will be identified. Death certificate information available from the national death registries includes the date and causes of death coded according to ICD-10. These data will be linked to the hospitalisation data to classify deaths as occurring inside versus outside the hospital setting. All patients in Denmark and Sweden will have information on in-hospital and out-of-hospital causes of death available for the entire covered population.
- Out-of-hospital coronary heart disease and cerebrovascular deaths will be considered confirmed if the underlying cause-of-death codes from the national death register are consistent with the codes in Table 2.

9.3.3 Other Variables

The study will define other variables that will be used to describe the study population and to control for confounding (using propensity scores). The availability of data on each variable will vary by data source (e.g., no or limited laboratory data are available in Sweden and Denmark). In Denmark and Sweden, outpatient diagnoses from hospital-based specialist outpatient clinics are available from the national patient registries. In general, in database analyses, the absence of information, such as an outpatient diagnosis, is classified as the absence of the condition. All patients without a dispensing for a medication are considered unexposed, and all patients without a diagnosis are considered as not having the condition.

Demographics

Data on the following demographic variables will be collected:

- Age
- Sex
- Calendar year of the index date
- Employment
- Years of education
- Duration of available history in the database up to the index date
- Duration of follow-up

Medical History

Medical history (yes/no) ascertained by outpatient (specialist, hospital outpatient) and/or hospital discharge diagnosis codes and/or prior medication dispensings recorded at any time before the index date:

- ADHD-related history:
  - Time since first ADHD diagnosis
  - Number of medical visits with ADHD listed as a diagnosis in the previous year

  - Number of previous ADHD regimens (treatments with different drug substances)
  - Duration of continued use of prior ADHD drugs
  - Use of multiple concurrent ADHD medications
- Cardiovascular disease: assessment of prior occurrence of study endpoints and broader subtype categories such as ischaemic heart disease, heart failure, and cerebrovascular disease
- Other diseases: hypertension (determined by the closest blood pressure measurements to the index date, when available), hyperlipidaemia, diabetes, renal disease, cancer
- Psychiatric comorbidities: mood disorders, anxiety disorders, eating disorders, or alcohol or substance abuse disorders
- Obesity
- Smoking-related disease (e.g., chronic obstructive pulmonary disease)

Use of Other Medications

Prior to index date:

- Use of "other ADHD medications" ever before, among both cohorts, and irrespective of being the dispensings that qualified for entry into the remote use of other ADHD treatments cohort
- Use of cardiovascular or antihypertensive medications within 6 months before the index date

9.4 Data Sources

To obtain sufficient study size and person-years of LDX use to address the objective, the study will be implemented in multiple health care data sources in European Union (EU) countries where LDX is expected to be approved for use in adult patients with ADHD. Individual studies will be conducted in each EU country according to a common core protocol. Data sources in the countries where the adult indication has been approved include Denmark and Sweden, where outpatient pharmacy-dispensed prescriptions, hospital diagnoses, and causes of death are available from national patient registries. No other EU countries had the adult indication approved at time this study was planned; therefore, data on adult use of LDX in other countries are not relevant in the current study. The data sources discussed in the following sections will be used to identify the cohort, exposures, outcomes, and risk factors of interest. Data available in each data source are summarised in Table 3.

9.4.1 Denmark

The Danish national databases of interest to this study are the Danish Civil Registration System, Danish National Patient Register, Danish Psychiatric Central Research Register, Danish National Prescription Register, and Danish Register of Causes of Death.

The Danish Civil Registration System, an administrative database that was established in 1968 (Schmidt et al., 2014), contains individual-level information on all persons residing in Denmark. By January 2014, it had cumulatively registered 9.5 million individuals. A unique 10-digit Civil Personal Register number is assigned to all persons and allows for the individual-level linkage of records in Danish registers. Information on migration and vital status, which is updated daily, allows for nationwide cohort studies with virtually complete long-term follow-up on emigration and death. These data have high accuracy and completeness and can be retrieved for research purposes.

The Danish health care system provides universal coverage to all Danish residents—5.6 million inhabitants (Eurostat, 2014). Health care coverage includes visits to general practitioners (GPs) and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health service. The Danish Civil Registration System allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries containing civil registration numbers, such as the Danish National Patient Register, Danish National Prescription Registry, and the Danish Register of Causes of Death. Data collected in these registries are available for research purposes. The process requires collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data (Danish Data Protection Agency, 2011; Danish Health and Medicines Authority, 2014). All applications have to be submitted in Danish.

Denmark's primary health care sector, which includes GPs, specialists, and dentists, generates about 96% of the prescription sales, most of which are reimbursable and are dispensed by community pharmacies. Each dispensing record contains information on the patient, drug, and prescriber. Dispensing records retain the patient's universal personal identifier, allowing for individual-level linkage to all Danish registries and medical databases.

The Psychiatric Central Research Register, established in 1970, provides data on treatments, diagnoses, and referrals for patients treated at psychiatric departments in Denmark (Mors et al., 2011). The International Classification of Diseases, 8th Revision (ICD-8) system was used until 1994, and ICD-10 thereafter. Quality assessment information concerning treatment of several mental disorders are made public every year. The nationwide registration of severe mental disorders is almost complete. However, most cases with mild to moderate mental disorders are managed by GPs or specialists in psychiatry working in private practice and are thus not registered in this database. Since 1995, data for this register have been collected by the Danish National Patient Register.

The Danish National Patient Register includes data on all hospital admissions since 1 January 1977 and on outpatient clinic and emergency department visits since 1995 (Lynge et al., 2011). Hospital discharge diagnoses and information on surgical procedures, in-hospital deaths, and some selected drugs are recorded. After 1993, hospital discharge diagnoses are coded using ICD-10 codes.

The Danish National Prescription Registry provides patient-level data on drug prescriptions dispensed by pharmacies since 1994 (Kildemoes et al., 2011). The National Prescription Registry collects data on reimbursed and unreimbursed drugs. This registry is administered by Statistics Denmark.

In Denmark, while the data on all-cause mortality comes from the Civil Registration System, the Danish Register of Causes of Death provides data on cause(s) of death for all deaths among citizens who died in Denmark since 1875, and since 1970 has computerised individual records. Classification of cause(s) of deaths is done in accordance to the WHO guidelines; since 1994, cause of death is recorded by ICD-10 codes. The quality of the register on causes of death relies mainly upon the correctness of the physicians' notification and the coding in the National Board of Health (Helweg-Larsen, 2011).

9.4.2 Sweden

The Swedish national databases of interest to this study are the Swedish National Patient Register, the Prescribed Drug Register, and the Causes of Death Register.

In Sweden, the national health care system provides universal coverage to all residents—9.6 million inhabitants (Eurostat, 2014). Health care coverage includes visits to GPs and specialists, hospital admissions, and hospital outpatient visits; drug costs are either partially or completely covered. A centralised Civil Registration System has been in place for many years, enabling personal identification of each person in the entire population and linkage to all national registers containing civil registration numbers (e.g., Swedish National Patient Register, cancer register, Prescribed Drug Register, Causes of Death Register and population registers) (Furu et al., 2010).

The Swedish National Patient Register covers all inpatient care in Sweden since 1964, with national coverage since 1987. The register includes information on diagnoses, surgical procedures, and in-hospital deaths. Since 2001, it also includes outpatient hospital care data. The register includes about 1.5 million discharges annually. Whereas coverage of the inpatient register is currently almost 100%, coverage of hospital-based outpatient care is not complete (about 80%) (Ludvigsson et al., 2011). Visits to GPs outside the hospitals are not included in the registers.

The Prescribed Drug Register provides patient-level data on all dispensed and prescribed drugs (reimbursed and unreimbursed) in ambulatory care to the whole population of Sweden since July 2005. The information on drugs includes drug substance, brand name, formulation and package, dispensed amount, dosage, expenditure and reimbursement, date of prescribing and dispensing, place of residence of the patient, practice issuing the prescription, and prescriber's specialty (Wettermark et al., 2007).

The Causes of Death Register records mortality data starting in 1961. It shows the underlying cause of death coded according to ICD-10 since 1997. The register includes all those who died during a given calendar year and were registered in Sweden at the time of death, regardless of whether the death occurred within the country (Socialstyrelsen, 2016).

Data requests for research purposes require collaboration with university or affiliated researchers and ethics committee approval.

Table 3. Main Features of Selected European Databases

Feature	Danish Patient and Prescription National Databases (N = 5,627,235)[a]	Swedish Patient and Prescription National Databases (N = 9,644,864)[a]
Database type	National health record databases capable of linkage with other databases through a unique personal identification number	National health record databases capable of linkage though the unique civil personal registration number
Database population	5.6 million (Eurostat, 2014)	9.6 million (Eurostat, 2014)
Proportion of the country's population covered by the database	100%	100%
Representativeness of patients	Total population covered	Total population covered
Data on medications	Pharmacy-dispensed prescriptions, reimbursed and unreimbursed since 1995	Pharmacy-dispensed prescriptions, reimbursed and unreimbursed; Since 2005
Dose	Formulation strength	Formulation strength
Duration	Based on pharmacy-dispensed prescriptions	Based on pharmacy-dispensed prescriptions
Drug dictionary codes/ therapeutic classification	ATC	ATC
Clinical indication	Not recorded; can be based on proxies	Not recorded; can be based on proxies
Outpatient diagnosis	Only outpatient hospital diagnosis in the National Patient Register	Only outpatient hospital diagnosis in the National Patient Register
Hospital diagnosis	Yes	Yes
Disease and procedures codes	ICD-10	ICD-10
Lifestyle risk factors	No	No
Data availability	Pharmacy-dispensed prescriptions, i.e., dispensings, since 1994; hospitals since 1977; outpatient hospital specialist clinics since 1995	Pharmacy-dispensed prescriptions, i.e., dispensings, since July 2005; hospitals since 1987; outpatient clinics since 2001
Approximate time lag (updates)	6-18 months but usually available at midyear	Usually available in Q3-Q4 of the following year

Feature	Danish Patient and Prescription National Databases (N = 5,627,235)[a]	Swedish Patient and Prescription National Databases (N = 9,644,864)[a]
Approval process for database research	Approval by Danish Data Protection Agency, Danish Health and Medicines Authority, and Statistics Denmark, depending on level and type of data	Data application and ethics committee approval required

ATC = Anatomical Therapeutic Chemical; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICD-10-CM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*.

[a] Population data from Eurostat (2014).

9.5 Study Size

The study size will be driven by the person-time at risk of current LDX use that will be available in the selected data sources during a defined study period. No dispensing of LDX prior to 2013 is recorded in these databases. Given the recent approval of Elvanse Adult®, it is not yet known how much time will be necessary in these countries to provide sufficient size for the study.

Table 4 shows the data on LDX utilisation among adults in Europe from a drug utilisation study conducted by IMS Health (2015) before the approval of Elvanse Adult®.

- Data from the Danish National Prescription Registry and the Danish National Hospital Registry showed that between March and December 2013, a total of 1,040 patients of all ages (138 aged 19-25 years and 329 aged > 25 years) received 3,111 dispensings for Elvanse. The average duration of exposure ranged between 73.8 and 76 days. The estimated total person-time of exposure among patients aged > 19 years in Denmark in 2013 and 2014 was 96.4 person-years (27.9 from those aged 19-25 years and 68.5 from those aged > 25 years).
- Data from the Swedish National Prescription Register showed that from March 2013 through December 2014, a total of 8,703 patients received 29,380 prescriptions of Elvanse; 5,195 of these patients (60%) were aged > 19 years. The mean duration of exposure among patients of all ages was 144.6 days. In Sweden in 2013 and 2014, the total person-time of exposure among patients aged > 19 years (estimated using the mean duration of exposure for all ages) was 2,058.1 person-years.

Table 4. Number of Adult Patients and Annual Duration of Use of Lisdexamfetamine, by Data Source

Data Source, Year	Age (Years)	Number of Patients	Duration of Exposure (in Days) Mean (SD) Median (Min; Max)	Calculated Average Daily Dose of Elvanse (mg) Mean (SD) Median (Min; Max)	Cumulative Person-Years[a]
Denmark, 2013[b]	19-25	138	73.8 (62.1) 62.7 (12.9; 286.3)	43.8 (14.3) 45.5 (7.1; 69.2)[c]	27.9
	> 25	329	76.0 (68.3) 54.6 (12.9; 412.1)	45.0 (15.1) 42.9 (13.6; 69.8)[c]	68.5
Sweden 2013	19-25	80	All ages 60.1 (34.3) 50 (12; 122)	All ages 42.7 (15.7) 30 (30; 70)	13.2
	> 25	302			49.7
Sweden 2014	19-25	1,167	All ages 141.2 (108.7) 106 (15; 365)	All ages 44.7 (15.5) 50 (30; 70)	451.5
	> 25	3,943			1,525.3
Sweden[d] 2013-2014	19-25	1,184	All ages 144.6 (115.9) 106 (15; 487)	All ages 44.6 (15.5) 50 (30; 70)	469.1
	> 25	4,011			1,589.0

RTI-HS = RTI Health Solutions; SD = standard deviation.

[a] Estimated by RTI-HS based on (number of patients * mean duration)/365.

[b] Data from the National Prescription Registry and the National Hospital Registry from March to December 2013.

[c] Data for all ages, based on 770 of the 3,111 dispensings.

[d] Cumulative data for the stated time period.

Source: IMS Health (2015).

Table 5 shows the estimated person-years of LDX current use needed to have an 80% probability that the upper limit of the 95% CI for the IRR for the MACE endpoint in the LDX new users cohort versus the remote use of other ADHD treatments cohort is less than 1.5 to 5 if the true IRR is 1.0, for MACE IRs ranging from 1 to 5 events per 1,000 person-years in the remote use of other ADHD treatments cohort. Calculations were made by using Episheet (Rothman, 2012b). For example, if the IR is 1 per 1,000 person-years, the true IRR is 1.0, and the LDX new users meeting study criteria have a total of 7,800 person-years of exposure, there is a probability of 80% that an IRR of 3.0 can be excluded.

Table 5. Estimated Number of Person-years Exposed to LDX Needed to Have an 80% Probability That the Upper Limit for the 95% Confidence Interval of the Incidence Rate Ratio Is Below 1.5, 2, 3, 4, or 5

Incidence per 1,000 Person-Years	Upper Limit for the 95% Confidence Interval of the Rate Ratio Is ...				
	1.5	2	3	4	5
1	57,240	19,590	7,800	4,900	3,640
2	28,590	9,790	3,900	2,450	1,820
3	19,040	6,520	2,600	1,630	1,210
4	14,270	4,890	1,950	1,230	910
5	11,410	3,910	1,560	980	730

IRR = incidence rate ratio; LDX = lisdexamfetamine dimesylate.

Note: The probability that the upper bound of the 95% confidence limit of the IRR is 1.5, 2, 3, 4, or 5 assumes that the true IRR is 1.0. Assumes a ratio of 5:1 comparator to lisdexamfetamine-exposed person-years.

Table 6 shows the estimated number of people exposed to LDX needed to have an 80% probability that the upper limit for the 95% CI of the IRR is below 1.5, 2, 3, 4, or 5 for average durations of LDX use of 75, 100, 200, and 300 days. For example, if the IR is 1 per 1,000 person-years and the true IRR is 1.0, we would need 37,986 patients with an average duration of LDX use of 75 days, 28,490 patients with an average duration of LDX use of 100 days, 14,245 patients with an average duration of LDX use of 200 days, or 9,497 patients with an average duration of LDX use of 300 days to have an 80% probability that an IRR of 3.0 can be excluded.

Table 6. Estimated Number of People Exposed to LDX Needed to Have an 80% Probability That the Upper Limit for the 95% Confidence Interval of the Rate Ratio Is Below 1.5, 2, 3, 4, or 5, by Average Duration of LDX Use

Average Duration of LDX Use	Incidence per 1,000 Person-Years	Upper Limit for the 95% Confidence Interval of the Rate Ratio Is Below:				
		1.5	2	3	4	5
75 days	1	278,759	95,403	37,986	23,863	17,727
	2	139,233	47,677	18,993	11,932	8,863
	3	92,725	31,752	12,662	7,938	5,893
	4	69,495	23,814	9,497	5,990	4,432
	5	55,567	19,042	7,597	4,773	3,555
100 days	1	209,069	71,552	28,490	17,897	13,295
	2	104,425	35,758	14,245	8,949	6,648
	3	69,544	23,814	9,497	5,954	4,420
	4	52,121	17,861	7,122	4,493	3,324
	5	41,675	14,281	5,698	3,579	2,666
200 days	1	104,535	35,776	14,245	8,949	6,648
	2	52,212	17,879	7,122	4,474	3,324
	3	34,772	11,907	4,748	2,977	2,210
	4	26,061	8,930	3,561	2,246	1,662
	5	20,838	7,141	2,849	1,790	1,333
300 days	1	69,690	23,851	9,497	5,966	4,432
	2	34,808	11,919	4,748	2,983	2,216
	3	23,181	7,938	3,166	1,985	1,473
	4	17,374	5,954	2,374	1,498	1,108
	5	13,892	4,760	1,899	1,193	889

IRR = incidence rate ratio; LDX = lisdexamfetamine dimesylate.

Note: The probability that the upper bound of the 95% confidence limit of the IRR is 1.5, 2, 3, 4, or 5 assumes that the true IRR is 1.0. Assumes a ratio of 5:1 comparator to lisdexamfetamine-exposed person-years.

During 2013 and 2014, LDX was not approved for adults, and after regulatory approval of LDX for adults, the actual use is expected to be greater than the projections listed here. The observed use of LDX in 2013 and 2014 suggests that after the adult indication is approved, it is not unreasonable to expect 1,500 person-years of LDX use across all the data sources per year. Thus, a study starting in late 2019 would have accumulated at least 2,154.5 person-years of LDX use from the years 2013 and 2014 (96.4 person-years in Denmark during 2013 and at least 2,058.1 person-years in Sweden) and would probably have more than 7,800 person-years of LDX use, assuming 1,500 additional person-years per year of LDX current use and accounting for the time lag of available data in each country. This would be in line with the 7,800 person-years needed to exclude an IRR above 3 with an 80% probability, if the IR in the remote use of other ADHD treatments cohort is 1 per 1,000 person-years (shown in Table 5).

9.6 Data Collection and Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all programs. Each database custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 Data Analysis

Database-specific analyses implemented by collaborating research centres will be conducted using SAS software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) for the analysis of the Danish and Swedish data. All analyses implemented by the coordinating centre will use SAS version 9.3 or higher.

This analysis section provides an overview of the analyses that will be conducted for this study. Data analyses will occur in three stages as follows:

1. A feasibility assessment that involves monitoring counts of adult LDX users in each data source will be performed annually; patient counts will be obtained from publicly available data sources in Denmark and Sweden: Medstats.dk in Denmark (The Danish Health Data Authority, 2015) and the Swedish drug database (Socialstyrelsen, 2014). These data will be reviewed by the research partners before submission to Shire for inclusion in the PBRERs.
2. A country-specific analysis performed by each of the database research partners that will create stratified tables with cross-classifications of patient and person-time counts by exposure category, endpoint, and quintiles of propensity scores.

3. A pooled analysis conducted at the coordinating centre, where summary data from the collaborating database research partners will be combined, as appropriate, to estimate overall measures of effect.

The database research partners have organisation-specific restrictions on the level and type of information that can be shared externally, and thus patient-level data cannot be combined across all data sources. This two-stage analysis is designed to comply with those restrictions while accomplishing the goal of assimilating the data from the collaborating database research partners into one summary analysis.

A core SAP will be developed separately and will describe methods for the creation of the study cohorts, the descriptive analyses, variable creation including propensity scores, and the IR and IRR analyses. The SAP will also detail the required input data from the individual database research partners that will be used to perform the pooled analysis. Calculation of person-years, IR and IRR, and CIs will be documented. A description of the planned pooled analyses and table shells will be included. Specification of the exact output tables to be provided by the coordinating centre will be included in the SAP. Appendices to the analysis plan will document all diagnosis, procedure, and medication codes to be used in defining the outcomes, exposures, and covariates. The core SAP will be adapted to the specifications of each database.

9.7.1 Country-Specific Analysis

Each database research partner will conduct country-specific analyses within each data source to (1) select the study population; (2) describe the study cohorts including patterns of LDX use among patients with cardiovascular diseases and hypertension, demographics, medical history, exposures, and endpoints; (3) estimate exposure propensity scores within its data; and (4) create a summary data set based on counts of patients, person-years, and outcome events according to the strata of propensity scores.

9.7.1.1 Select Study Population

Each database research partner will first apply the study inclusion/exclusion criteria to select the study population. During this process, each database research partner will create a table showing the impact that each step of applying the study criteria has on the study size, including the number of excluded LDX users and reasons for exclusion. Once the study population has been identified, members of each study cohort will be described as of the index date.

9.7.1.2 Descriptive Analysis of Study Cohorts

For each exposure cohort (LDX cohort and remote use of other ADHD treatments cohort), and within each data source, characteristics of all variables of interest (see also Section 9.3) will be described for each cohort: mean (standard deviation [SD]), median (25th percentile, 75th percentile), and frequency distribution for continuous variables and number and percentage for categorical variables.

Use of LDX and Other Medications

Prior to the index date

1. "Other ADHD treatments" that qualified for remote use cohort entry; number and proportion of patients in each ADHD drug subtype
2. Use of "other ADHD medications" ever before, among both cohorts, and irrespective of being or not the dispensings that qualified for remote use cohort entry; number and proportion of patients in each ADHD drug subtype; and total number of dispensings ever before by categories

During follow-up

Patterns of LDX and other drug use during follow-up will be described, including description of days' supply; dose; number of LDX dispensings; and duration of use of LDX, when possible (see also Section 9.3.1, Exposure Assessment). Differences in dispensing patterns between countries will be described and taken into account in the analyses, if needed.

Descriptive Analysis of Study Endpoints

For each endpoint, the number of patients identified as individuals falling into each category of the endpoints of interest will be summarised. Categories of interest are the final case classification and sources of information utilised to reach the classification. Additional categories will include subcategories of current LDX use and post-LDX use; sex and age categories; and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions.

9.7.1.3 Estimation of Propensity Scores

Within each data source, person-time and endpoint counts for each cohort will be stratified into quintiles of propensity scores. Stratifying on the quintiles of the propensity score eliminates approximately 90% of the bias due to measured confounders when estimating a linear treatment effect (Austin, 2011). Increasing the number of strata used should improve bias reduction, although a point is reached at which the marginal reduction in bias decreases as the number of strata increases (Austin, 2008). The propensity score will serve as a within–data source variable that summarises the confounding from a large set of variables. The covariates of interest that will be evaluated for potential inclusion in the propensity score estimation will be those in Section 9.3.3. Data aggregated by strata of propensity scores estimated in each data source will be used to estimate overall effects across all of the data sources in the pooled analysis (See Section 9.7.2).

Within each data source, propensity scores will be estimated using unconditional logistic regression. Propensity scores will estimate the probability that a given patient will receive LDX, as opposed to being in the remote use of other ADHD treatments cohort, conditional on measured covariates and can serve as a summary confounder variable. Quintiles of propensity scores will be defined by the distribution of propensity scores for the LDX cohort. Details of the propensity score procedures will be provided in the SAP.

9.7.1.4 Create a Summary Data Set

Each collaborating centre will create summary tables based on counts of patients, person-years, and outcome events according to the strata of age categories (18-34, 35-44, 45-64, 65+ years), sex, propensity score quintiles, and other variables of interest such as those specified in the secondary sensitivity analyses (LDX duration, concomitant use of other ADHD medications) and exploratory analyses (e.g., dose of LDX, previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions). Strata may need to be collapsed depending on the number of events. Specific table shells will be included in the SAP.

9.7.2 Pooled Analysis

Using propensity score–stratified tables with aggregated data from each database research partner, the coordinating centre will conduct an analysis of the data from each individual data source and an overall analysis combining the data across all data sources, if appropriate. Data-source-specific and pooled analysis activities will include estimation of crude and adjusted IRs, and analysis of crude and adjusted IRRs using Poisson regression models.

9.7.2.1 Pooled Description of Study Cohorts

After receiving the site-specific description of study cohorts, the coordinating centre will pool the data from all data sources, when possible (i.e., rates and effect estimates are reasonable and consistent between databases), and describe for each exposure cohort (i.e., the LDX cohort and remote use of other ADHD treatments cohort) the characteristics of all variables of interest: mean (SD), median (25th percentile, 75th percentile [or range]) and frequency distribution for continuous variables, and number and percentage for categorical variables.

9.7.2.2 Analysis of the Crude and Adjusted Incidence Rates

Crude and adjusted (by propensity score quintiles) IRs will be estimated within each data source and overall across data source, using the event counts and person-time provided by each of the collaborating centres. Crude IRs will be calculated as the number of outcome events divided by the person-time at risk in each cohort. The Poisson distribution will be used to calculate exact 95% CIs for the IRs.

Adjusted IRs will be estimated in each data source using the event counts and the person-time in each centre-specific quintiles of propensity scores in each cohort. Additionally, pooled adjusted IR and 95% CI over all data sources will be estimated. Poisson regression models will be used.

The analysis of crude and adjusted IRs by and propensity score will include the following:

- Crude and adjusted IR by propensity score quintiles for all primary and secondary endpoints during current LDX use and during follow-up of the remote use of other ADHD treatments cohort, in each data source and combined for all data sources.
- Crude and adjusted IR by propensity score quintiles for MACE by subcategories of LDX duration and dose; by subcategories of concomitant use of other ADHD medications during current LDX use ("current single LDX use" and "current LDX multiple drug use"); and stratified by sex, age categories (stratification by sex and age for the crude IRs only), and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions.
- Crude and adjusted IR by propensity score quintiles for MACE using other definitions of LDX time at risk (e.g., post-LDX time at risk or extended current use carryover period), as described in the sensitivity analysis section (Section 9.7.3).

9.7.2.3 Analysis of Incidence Rate Ratios

Crude IRRs will be calculated as the crude pooled IR in the LDX cohort divided by the crude pooled IR in the remote use of other ADHD treatments cohort. Poisson regression methods will be used to estimate the adjusted IRR and 95% CIs within each data source. Combined IRR and 95% CI will be estimated using a random effect Poisson regression model with data source as the random effect and adjusting for propensity score quintiles.

In each data source and when calculating a combined IRR for all data sources, estimation of IRRs will include the following components:

- IRRs of all endpoints comparing current LDX use with remote use of other ADHD treatments.
- IRR of MACE among long-term LDX users (current LDX users with ≥ 12 months cumulative exposure to LDX, that is, those with ≥ 12 months duration of current LDX use) compared with remote users of other ADHD treatments without exposure to these treatments for a period of at least 12 months after the index date (long-term remote users).
- IRRs of MACE by subcategories of LDX use by subcategories of concomitant use of other ADHD medications during current LDX use ("current single LDX use" and "current LDX multiple drug use").
- Exploratory analyses of endpoints: IRRs of MACE comparing current LDX use with remote use of other ADHD treatments stratified by LDX dose, sex, age categories, and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions.
- As described in the sensitivity analyses (Section 9.7.3): IRRs of MACE comparing LDX use using other definitions of LDX time at risk (e.g., post-LDX use risk, extended current use lag time and carryover period) and outcome categories (e.g., including secondary discharge diagnosis), versus remote use of other ADHD treatments.

9.7.3 Sensitivity Analyses

Impact of Study Eligibility Criteria

Due to the differences in study inclusion criteria between the LDX cohort and the remote users of other ADHD medication cohort, a sensitivity analysis will be performed in which the same eligibility criteria are applied to both cohorts to estimate IRs and IRRs of MACE comparing current LDX use with remote use of other ADHD treatments under these conditions.

Impact of Previous Exposure

The impact of recent prior exposure to ADHD medications in both exposure groups will be evaluated in this sensitivity analysis. While the remote user cohort inclusion criteria specify that the patient cannot have had ADHD medication exposure within at least 180 days before the index date, the LDX user cohort does not have this criterion. The IR and IRR of MACE comparing the current LDX user cohort versus the remote user cohort will be estimated separately for each of the following categorisations of LDX users: with and with no previous use of other ADHD medications within at least the last 180 days before the index date.

Impact of Exposure Time

Sensitivity analyses including estimation of IR and IRRs of MACE comparing current LDX use versus remote use of other ADHD treatments will be conducted by extending the current use carryover period and the allowed gaps between dispensings from 30 days to 60 days, thus lengthening the definition of current exposure to end 60 days after the estimated end of the last dispensing for LDX. Accordingly, discontinuation will be redefined by assuming that each dispensing lasts until the specified extended duration (60 days) after each dispensings' days' supply.

To evaluate whether there is a delayed cardiovascular effect of LDX exposure, a sensitivity analysis will be performed using the time of post-LDX use versus the remote use of other ADHD treatments cohort. To evaluate the potential effect of exposure to "other ADHD treatments" in the comparison between post-LDX use versus remote use of other ADHD treatments, an additional secondary analysis will be performed using the time of "post-LDX use, no drug use" and time of "post-LDX use, with other ADHD drug use" as time at risk, respectively.

Finally, a sensitivity analysis will include time at risk from post-LDX use and from current LDX use in an intention-to-treat analysis.

Impact of Outcome Categories

An additional subgroup analysis including both primary and secondary discharge diagnoses for the MACE endpoint of interest in Denmark and Sweden will be conducted. This analysis will include all cases identified by primary and secondary discharge codes.

Unmeasured Confounding

It is possible that final relative risk estimates in any study could be confounded by variables that could not be measured or could not be measured accurately in one or more cohorts. This is often a concern in studies based on secondary data. To assess the potential impact of unmeasured confounding on the results in this study, a bias analysis will be implemented (Savitz and Baron, 1989). In this analysis, a range of plausible hypothetical values for the prevalence of the unknown confounder among the exposed and among the unexposed and for the IRR of the unknown confounder and the outcome of interest (e.g., 2 to 3) is applied to assess the hypothetical potential impact of an unknown confounder on the overall IRR. Such analyses show the magnitude of the difference in the prevalence of a confounder between exposed and unexposed groups and the strength of relationship between the confounder and the outcome that is needed to substantially influence the study result.

9.7.4 Methods for Handling Missing Data

In this study, as in most of the studies performed in automated health databases, all patients without a dispensing for a medication will be considered unexposed, and all patients without a diagnosis will be considered as not having the condition.

When presenting results stratified on a single variable, patients missing the variable value will be reported as a separate category. For modelling (i.e., when computing exposure propensity scores), variables with a significant amount of missing data (e.g., > 10%) may be imputed. The frequency of missing information will be shown in the descriptive analysis. For the unconditional logistic regression used to estimate the propensity scores (Section 9.7.1.3), confounders with a significant amount of missing data may be imputed, and the method of imputation will be described in the SAP.

9.7.5 Content of Reports

Information regarding the annual monitoring of adult LDX users will be included in the PBRER. The annual counts will be used to determine the timing of analyses and the full study report.

The full study report will describe the cohorts and the results of all analysis. All pooled IRRs will be standardised for propensity score category and data source. All sensitivity analyses will be included.

9.8 Quality Control

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

At a minimum, all programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. Appropriate data storage and archiving procedures will be followed (e.g., storage on CD-ROM and DVD), with periodic backup of files. Standard procedures will be in place to restore files in the event of a hardware or software failure at each research centre.

All key study documents, such as the analysis plan and study reports, will undergo quality control review, senior scientific review, and editorial review.

Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (ISPE, 2015).

A quality assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

9.9 Limitations of the Research Methods

The relevant parameters to consider for the interpretation of the results focus on the point estimate, the upper limit of the 95% CI, and the absolute excess risk. A limitation of the study is the potential low precision of the estimated relative risks for the study endpoints. We estimate that for MACE in the whole population there is an 80% probability that the upper limit of the 95% CI of the observed rate ratio is below 3 if the IR is 3 per 1,000 person-years, the true IRR is 1.0, and the LDX new users meeting study criteria have 7,800 person-years of exposure. However, 19,590 person-years of exposure will be needed to estimate with an 80% probability that the upper limit of the 95% CI of the observed rate ratio is below 2. In terms of absolute risk, a 95% CI upper limit of 3 translates to an increase of about two additional cases per 1,000 person-years of treatment. Although precision may be low, with findings that are compatible with high multiples of risk, the risk is very low for this outcome, and even a multiple of 3 in the rate would correspond to a small absolute increase in risk for MACE. The rate of MACE in the population treated for ADHD (predominantly young adults) is expected to be low. By using multiple data sources, we intend to accrue patient experience more quickly than would be possible using a single data source. There will be some heterogeneity across data sources, which may impact the precision of estimates. The study population size may also limit the ability to evaluate differences in risk across patient subgroups. As with any database study, the actual study size will be determined by the utilisation of the drug of interest and the inclusion/exclusion criteria. Additional rounds of analyses can be implemented as the available number of patients increases, and we will continue to evaluate the feasibility of extending the study to other data sources.

The Danish National Patient Register and the Swedish National Patient Register are based on diagnoses when patients are discharged from the hospital or in connection with a hospital outpatient clinic visit. Ascertainment of covariates using hospital discharge diagnoses might result in the identification of individuals with more severe comorbidity. In addition, there may be differences in the dispensing patterns between countries due to different treatment guidelines, country-specific recommendations, or public health systems. These different dispensing patterns may lead to different mean doses and

durations of use in each country. The effect of different doses and durations of use on the risk of the outcomes of interest will be evaluated as one of the secondary objectives.

Because of the serious nature and clinical guidelines for the management of the acute cardiovascular events of interest, hospitalisation is expected for most of the non-fatal events under study. The selected data sources for this study have been shown to reliably capture and classify hospitalisations for cardiovascular conditions. All data sources will be able to capture conditions and deaths that occur in a hospital. It has been shown that, in general, misclassification of outcomes that do not differ by exposure will underestimate the incidence ratio. However, the impact is expected to be small because validation studies of these outcomes have shown that identification of the cardiovascular outcomes of interest is quite reliable in the planned data sources.

Information on other covariables, including cardiovascular risk factors, is limited to information available in the data source; thus, surrogates for smoking and obesity will be used. Use of over-the-counter medications will not be captured. There is no reason to believe that completeness of historical information would differ between the two study exposure cohorts; therefore, any misclassification would not be differential.

We assumed that LDX and other ADHD medications are prescribed only for ADHD and that members of these cohorts are not required to have a recorded diagnosis of ADHD. However, some patients may have been prescribed these medications for other conditions, such as narcolepsy. Depending on the number of patients that may be prescribed these medications for other diseases, we will minimise the inclusion of these patients by excluding them from the patient population, when possible. Bias from misclassification of ADHD among these patients could be present if the risk of MACE associated with other indications or reasons for prescription of stimulants differs from the risk associated with ADHD. The magnitude of the bias is expected to be low given the low expected proportion of patients prescribed LDX and other ADHD drugs for diseases other than ADHD. In addition, patients taking LDX could be more severely affected than those in the remote use of other ADHD treatments cohort. Determination of severity or duration of ADHD will be a challenge. Clinical data on ADHD are frequently not available in hospital-based data sources, and many adult patients may not be treated unless their disease is severe. There is little evidence that ADHD or that ADHD severity is independently associated with an increased risk for MACE. The matching and propensity score approaches will limit the effect of any confounding. In addition, in Denmark, amphetamine and dexamphetamine are available only via magistral prescriptions (produced by a specialised pharmacy) and are not routinely recorded, leading to misclassification of exposure among remote users of other ADHD treatments; however, utilisation of these drugs to treat ADHD is expected to be low (Pottegård et al., 2012).

Determining exposure duration in an accurate manner can be a challenge with secondary health care data. Once a dispensing appears in the data, we assume that the patient takes the product as dispensed. However, we have no direct measure of patient adherence. It is possible that patients in either cohort will stop medication prematurely and/or reserve medication to take at a later time, resulting in misclassification of exposure. Therefore, we will extend the time at risk to 30 days following the end of the

dispensing period to account for possible variation in adherence and will evaluate in sensitivity analyses a longer period (60 days after the end of the dispensing period).

10 Protection of Human Subjects

This is a non-interventional, population-based study of secondary data and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each research partner will apply for an independent ethics committee review according to local regulations.

Country-specific data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

11 Management and Reporting of Adverse Events/Adverse Reactions

11.1 Studies Using Secondary Data

Based on current guidelines from ISPE (ISPE, 2015) and the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP)* (EMA, 2014), non-interventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require expedited reporting of adverse events/reactions (EMA, 2014; ISPE, 2015).

12 Plans for Disseminating and Communicating Study Results

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the risk management plan, PBRER, and other regulatory milestones and requirements. Study reports will be prepared using a template following the *Guideline on Good Pharmacovigilance Practices (GVP)* Module VIII Section B.6.3 (EMA, 2017).

In its *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, the ISPE contends that “there is an ethical obligation to disseminate findings of potential scientific or public health importance” (ISPE, 2015); for example, results pertaining to the safety of a marketed medication. Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2018). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (von Elm et al., 2008). The Consolidated Standards of Reporting Trials statement (Schulz et al., 2010) refers to randomised studies, but provides useful guidance applicable to non-randomised studies as well.

Communication via appropriate scientific venues (e.g., ISPE) will be considered.

The marketing authorisation holder and the investigators will agree upon a publication policy: the principal and coinvestigators will coauthor scientific manuscript(s) of the results to be published, irrespective of data ownership. Each research partner has the right to publish country-specific results. The marketing authorisation holder will be entitled to view the results and interpretations included in the manuscript(s) and provide comments prior to submission of the manuscript(s) for publication (EMA, 2013).

13 Other Good Research Practice

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (ISPE, 2015) and has been designed in line with the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2017*)*. The *ENCePP Checklist for Study Protocols* (ENCePP, 2018a) has been completed (see Annex 2).

The study is a postauthorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004) and provided in the EMA *Good pharmacovigilance practices (GVP) Module VIII: Post-Authorisation Safety Studies* (EMA, 2017), and with the 2012 EU pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2012). The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.1. “Progress Reports” and VIII.B.6.3.2. “Final Study Report” of the *Guideline of Good Pharmacovigilance Practices* EMA (2013).

The study has been registered in the ENCePP EU PAS Register (European Union electronic register of postauthorisation studies) (ENCePP, 2018c) (EUPAS20546). The research team and study sponsor will adhere to the general principles of transparency and independence in the ENCePP Code of Conduct (ENCePP, 2018b).

14 References

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2.
ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 section number 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). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the *Guidance and Module VIII of the Good Pharmacovigilance Practices (GVP).*

Study title:

Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments

EU PAS Register® number: SPD489-825

Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.2 End of data collection[1]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Monitors of adult LDX users will be done annually starting in 2016.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1.
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4 and 2.1.5 Rather than formal hypothesis testing we will describe the effect measure and confidence interval, adjusting for potential confounders.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1.2, 9.1.3
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.2, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8, 9.7.2.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8, 9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☒	☐	

Comments:

[1] Date from which the analytical data set is completely available.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.2
4.2.2 Age and sex	☒	☐	☐	9.3.3
4.2.3 Country of origin	☒	☐	☐	9.3.3
4.2.4 Disease/indication	☒	☐	☐	9.3.3
4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1.3, 9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	Annex 3

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7.3
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.7.3
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.3

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

No effect modifiers have been identified a priori.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3, 9.4
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2, Annex 4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Study investigators will review results, as will regulatory agencies. In addition, a manuscript describing the study results will be submitted to a peer-reviewed medical journal.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1.3, 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Cristina Rebordosa

Date: dd/Month/year

Signature: _____

Comments:

Name of the main author of the protocol: Cristina Rebordosa

Date: _____

Signature: _____

Annex 3.
Validity of Endpoint Definitions

Hospitalisations for Acute Myocardial Infarction

Acute myocardial infarction (AMI) will be identified by hospital discharge diagnosis codes. Data from the mortality registers will be used to classify deaths as occurring inside versus outside the hospital setting. Positive predictive values to identify AMI ranged from 92% to 97% in the Danish National Patient Registry (Sundbøll et al., 2016) and from 98% to 100% in the Swedish National Patient Register (Ludvigsson et al., 2011).

Hospitalisations for Stroke

Stroke acute events, either of ischaemic or haemorrhagic vascular aetiology, will be identified by hospital discharge diagnosis codes.

Data from the mortality registers will be used to classify deaths as occurring inside versus outside the hospital setting. Prior validated algorithms to identify ischaemic strokes and cerebrovascular events can be used (Ray et al., 2009; Roumie et al., 2008). The PPV to identify stroke and TIA in the Swedish National Patient Register was 99% (Ludvigsson et al., 2011).

Hospitalisation for Unstable Angina

Prior studies have investigated the validity of algorithms to identify unstable angina. Sundbøll et al. (2016) performed a validation study of cardiovascular diagnoses in the Danish National Patient Register (Sundbøll et al., 2016). Unstable angina was identified with I20.0 International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code as a hospital discharge diagnosis and found a PPV of 88%. Joensen et al. (2009) researchers identified patients participating in the “Diet, Cancer, Health” cohort study who had a first-time primary or secondary hospital discharge diagnosis of unstable angina (ICD-10 code: I20.0) in the Danish National Patient Registry between 1993 and 1997 (Joensen et al., 2009). During validation, events were classified in accordance to American Heart Association and European Society of Cardiology criteria (Luepker et al., 2003). Verified events were classified as definite MI (fatal and non-fatal events), probable MI, possible MI, unstable angina pectoris, and medical procedure-related event. The PPV for unstable angina was 27.5%; PPVs were higher for MI (81.9%). The PPVs were also higher among patients diagnosed in a ward than in those diagnosed in the emergency department or at the outpatient clinic (for unstable angina discharged from ward, the PPV was 42%). The PPV for acute coronary syndrome among men was 72.6% (vs. 50.1% among women). The PPV for acute coronary syndrome identified through primary discharge diagnosis was 67.1% (vs. 47.0% for secondary discharge diagnosis). In Sweden, as part of broader study to

evaluate the reliability of the Swedish inpatient registry, primary diagnoses of angina pectoris were ascertained, and 18 of the 19 cases (PPV = 95%) identified were confirmed through review of medical charts (Ludvigsson et al., 2011). A cohort study performed in the Canada Saskatchewan Health beneficiaries' database identified all patients aged 40 to 84 years with a hospital primary discharge International Classification of Diseases, 9th Revision (ICD-9) code 410 (n = 2,260) or code 411 (n = 799), between 1999 and 2001 (Varas-Lorenzo et al., 2008). The Braunwald criteria (Braunwald, 1989) were used to classify unstable angina according to angina class severity and clinical circumstances. Among the 763 validated cases with a discharge code of 411, 561 (73%) were classified as unstable angina/intermediate coronary syndrome, leading to a PPV for 411 to identify unstable angina of 73% (95% CI, 70%-77%) (Varas-Lorenzo et al., 2008).

Hospitalisation for Transient Ischaemic Attack

Two studies have evaluated the validity of the transient ischaemic attack (TIA) diagnosis in the Danish National Patient Register. TIA was defined as first-time primary or secondary hospital discharge diagnosis of TIA (ICD-10 code: G45). Both studies included a small number of TIA events. Validation consisted of medical chart review. Johnsen et al. (2002) considered TIA as confirmed based on the Kraaijeveld criteria which include assessment of the time course of TIA, symptoms of carotid TIA (hemiparesis, aphasia, and amaurosis fugax), symptoms of vertebrobasilar TIA (such as bilateral, basculating, or alternating weakness or sensory symptoms, transient global amnesia) or symptoms of uncertain territory TIA (hemianopia and dysarthria), and symptoms explicitly not acceptable as TIA (Kraaijeveld et al., 1984). Krarup et al. (2007) considered TIA confirmed with the following definition: temporary and focal cerebral dysfunction of presumed vascular origin which lasted no more than 24 hours and left no sequelae (NINDS, 1975). The PPV values for the studies performed in the Danish National Patient Registry ranged from 57.9% to 68.4% (Krarup et al., 2007). In the study by Johnsen et al. (2002), the proportion of verified diagnoses (PPV) by type of department for TIA was 46.7% in the emergency department, 67.4% in the non-specialty departments, and 62.2% in the specialty departments; for ischaemic stroke, 40% in the ER, 87% in the non-specialty departments, and 90.6% in the specialty departments. There was high availability of data on complementary tests, such that the basis for a verified diagnosis of TIA came from computed tomography/MRI scans, 81.4%; ultrasonography, 73.7%; angiography, 5.1%; and echocardiography, 29.7%. Autopsy was conducted in only 5 of 21 fatal cases (23.8%) (Johnsen et al., 2002). One study evaluated the validity of an inpatient diagnosis of TIA recorded in the Swedish inpatient registry, and although the ICD-8 and ICD-9 codes used to define TIA and the definition used to consider TIA confirmed were not provided, the authors reported that after medical record review, 74.2% of the cases of TIA were confirmed (Lindblad et al., 1993). A recent systematic review of validated methods for identifying cerebrovascular accident and TIA using administrative data from the US and Canada found seven manuscripts that evaluated ICD-9 or ICD-10 codes, most frequently ICD-9 code 435 and ICD-10 code G45 (Andrade et al., 2012). Most studies were limited to inpatient data. Validation was performed most frequently by review of medical charts, and the confirmation criteria varied. In three of the seven studies evaluating ICD-9 code 435, the PPVs were 70% or higher. Three

studies evaluating ICD-9 435 code reported PPVs of 28% to 33%. In the only study that evaluated ICD-10 codes, the PPV of ICD-10 codes G45.x (97%) was found to be higher than the PPV of ICD-9 codes 435.x (70%). Limited data suggest that the PPV may be higher for algorithms using a primary discharge diagnosis only and when using inpatient rather than outpatient diagnoses.

Serious Ventricular Arrhythmia and Sudden Cardiac Death

Hospitalisations for ventricular cardiac arrhythmias and cardiac arrest have a high PPV and are useful for selecting events in epidemiological studies on drug-induced arrhythmias (De Bruin et al., 2005; Johannes et al., 2010; Roumie et al., 2008)).

In an observational cohort study by Chung et al. (2010), sudden cardiac death was defined as a sudden pulseless condition (arrest) that was immediately fatal (or rarely resuscitated with death in 48 hours) and was consistent with a ventricular tachyarrhythmia occurring in the absence of a known non-cardiac condition as the proximate cause of the death. The PPV of the entire study sample identified through the codes listed in Table 2 of the current protocol, was 76.2%, but when additional restriction criteria were used the PPV increased to 79.6% if no evidence of a terminal institutional stay, 85.1% if underlying cause of death code consistent with sudden cardiac death, and 86.0% if no terminal procedures inconsistent with un-resuscitated cardiac arrest (Chung et al., 2010).

Out-of-Hospital Coronary and Cerebrovascular Deaths

All deaths occurring during the study will be identified. Mortality data will be linked to the hospitalisation files to classify deaths as occurring inside versus outside the hospital. The underlying cause of death coded in the national death register file takes into account additional information provided by medical practitioners or coroners after the death has been registered. The classification and inclusion of events based only on hospitalisations will be most homogeneous across the included data sources in this study; however, a consequence will be the incomplete ascertainment of these events as approximately one-third of patients with an AMI die suddenly before arriving at the hospital (Rothwell et al., 2005). Historically, deaths occurring outside a hospital setting frequently have not been ascertainable in database studies and therefore have not been included in such studies' primary endpoints. We will identify out-of-hospital deaths where information on out-of-hospital deaths is available through recorded causes from death certificates or direct linkage to the national mortality registry.

Out-of-Hospital Coronary Heart Disease Death

Out-of-hospital deaths from coronary heart disease are defined as sudden cardiac death (SCD) or deaths due to AMI in persons dying outside a hospital setting. These will be ascertained through diagnoses recorded on autopsy reports and death certificates, as available, using a published validated computerised definition (Chung et al., 2010).

Events identified as out-of-hospital deaths must meet the following criteria:

- Have on the death certificate an underlying cause of death that is compatible with SCD or fatal AMI (Chung et al., 2010; Ray et al., 2009); the codes provided in Table 2 have been reported with a high PPV for SCD and AMI
- Have no terminal hospitalisation
- Have a place of death that is not a hospital institution

Out-of-Hospital Death from Cerebrovascular Diseases

A similar approach will be used to identify out-of-hospital cerebrovascular deaths based on available information. Previously validated algorithms to identify strokes (including cerebrovascular death) will be used (see Table 2).

Annex 4.
ICD-10 Codes and ICD-10 Terms for Study Endpoints

ICD-10 Code[a]	ICD-10 Term
Hospitalisation for AMI, fatal or non-fatal	
I21	Acute myocardial infarction
Hospitalisation for unstable angina	
I20.0	Unstable angina
Hospitalisation for stroke, fatal or non-fatal	
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
H34.1	Central retinal artery occlusion
Hospitalisation for transient cerebral ischaemic attack (TIA)	
G45	Transient cerebral ischaemic attacks and related syndromes
Hospitalisation for SVA/SCD	
I46.0	Cardiac arrest with successful resuscitation
I46.1	Sudden cardiac death, so described
I46.9	Cardiac arrest, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
R96.0	Instantaneous death
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death
Coronary and cerebrovascular deaths out-of-hospital	
AMI/coronary heart disease death, including SCD	
I10	Essential (primary) hypertension
I11.9	Hypertensive heart disease without (congestive) heart failure
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction

ICD-10 Code[a]	ICD-10 Term
I23	Certain current complications of acute myocardial infarction
I24	Other acute ischemic heart diseases
I25	Chronic ischemic heart disease
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, unspecified
I46.0	Cardiac arrest with successful resuscitation
I46.1	Sudden cardiac death, so described
I46.9	Cardiac arrest, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
I49.8	Other specified cardiac arrhythmias
I49.9	Cardiac arrhythmia, unspecified
I51.6	Cardiovascular disease, unspecified
I51.9	Heart disease, unspecified
I70.9	Generalised and unspecified atherosclerosis
R96.0	Instantaneous death
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death
Coronary and cerebrovascular deaths out-of-hospital	
Stroke/cerebrovascular deaths	
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
H34.1	Central retinal artery occlusion
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
G45	Transient cerebral ischaemic attacks and related syndromes
R96.0	Instantaneous death
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death

AMI = acute myocardial infarction; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision;* SCD = sudden cardiac death; SVA = serious ventricular arrhythmia; TIA = transient ischaemic attack.

[a] This code list will be adapted to each data source.