PASS Information

Title	Post-authorization Safety Study Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder: Core Common Protocol Protocol No. [178-CL-114]
Study identifier / Protocol number	*EU PAS register number:* To be registered prior to data collection start
Protocol version & date of last version of protocol	Version: 9.0 Date: 10 November 2016
Active substance	Mirabegron
Medicinal product	Betmiga (EU) Myrbetriq (US)
Product reference	NDA number 202611 EU/1/12/809/001-018
Procedure number	EMEA/H/C/002388
Marketing authorization holder(s)	Astellas Pharma Global Development, Inc.
Joint PASS	☐ Yes ☒ No

Research question and objectives	The primary objectives of this study are:
	• To estimate and compare the incidence of cardiovascular (CV) outcomes within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to antimuscarinic medications (as a group) used in the treatment of overactive bladder (OAB). Outcomes include acute myocardial infarction (AMI), stroke, CV mortality, all-cause mortality and a composite measure of major adverse cardiovascular events (MACE), defined as the first of AMI, stroke, or CV mortality.
	• To estimate the effect above among patients ages 65 years and older.
	• To estimate the effect above among patients at high risk for CV events.
	• To estimate the effect above among naïve new users and non-naïve new users of mirabegron or antimuscarinic medications.
	
	The secondary objectives of this study are:
	• To estimate and compare the incidence of CV outcomes within *current* exposure to mirabegron and *current* exposure to antimuscarinic medications (as a group) in intervals of time since initiation (i.e., < 60 days, 60 to < 120 days, 120 to < 180 days, >=180 days).
	• To estimate and compare the incidence of CV outcomes within categories of recency of use:
	  ○ *recent* exposure to mirabegron vs *past* mirabegron exposure.
	  ○ *current* exposure to mirabegron vs *past* mirabegron exposure.
	  ○ *recent* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group) .
	  ○ *current* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group).
	• To estimate and compare the effect of cumulative dose across tertiles (*current* exposure only) of mirabegron dose.
	• To estimate and compare the effect of cumulative dose across tertiles (*current* exposure only) of antimuscarinic medication dose, restricted to the most commonly observed medication in each data source.
	• To estimate and compare the incidence of CV outcomes

	within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to each *individual* antimuscarinic medication (where sample size allows).
Countries of study	United Kingdom, United States (2 data sources), Denmark, and Sweden
Number of Sites or Data Sources	5 research partners (each focusing on different data sources)
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Marketing authorization holder

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1 PROTOCOL TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF KEY TERMS

AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CDC	Centers for Disease Control and Prevention
CDR	Cause of Death Register (Sweden)
CHD	Coronary Heart Disease
CHI	Comprehensive Health Insights
CPE	Centre for Pharmacoepidemiology
CPR	Central Person Registry (Denmark)
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
DAMD	Danish General Practitioner Database
DDD	Daily Defined Dose
DNPR	Danish National Patient Register
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration (US)
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GPRD	General Practice Research Database
GVP	Good Pharmacovigilance Practices
HES	Hospital Episode Statistics
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
ISAC	Independent Scientific Advisory Committee (of CPRD)
ISPE	International Society for Pharmacoepidemiology

KI	Karolinska Institute
LOINC	Logical Observation Identifiers Names and Codes
MACE	Major Adverse Cardiovascular Event
MAH	Marketing Authorization Holder
MHRA	Medicines and Health Care Products Regulatory Agency
MI	Myocardial Infarction
NCSP	Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures
NDA	New Drug Application
NDI	National Death Index
NHS	National Health Service
NPR	National Patient Register (Sweden)
OAB	Overactive Bladder
ONS	Office for National Statistics
ORD	Optum Research Database
PASS	Post-Authorization Safety Study
PB	Privacy Board
PDR	Prescribed Drug Register (Sweden)
PHIVE	Protected Health Information and Vendor Ethics Committee (Humana)
PMR	Post Marketing Requirement
PPV	Positive Predictive Value
PS	Propensity Score
PTCA	Percutaneous Transluminal Coronary Angioplasty
RR	Relative Risk
RTI-HS	RTI Health Solutions
SAB	Scientific Advisory Board
SAP	Statistical Analysis Plan
SDU	University of Southern Denmark
SOP	Standard Operating Procedure
SSA	Social Security Administration
THIN	The Health Improvement Network
UK	United Kingdom
US	United States

List of main key terms unique in the study protocol

Terms	Definition of terms
New users	Patients who receive a prescription or dispensing for mirabegron or any specific antimuscarinic medication during the study period without a prescription or dispensing for the same medication in the previous 12 months. This definition permits patients to either be **naïve new users** or **non-naïve new users** depending on whether they had a prior prescription or dispensing for another overactive bladder (OAB) medication.
Naïve new users	Patients with a new prescription/dispensing of an OAB medication (mirabegron or an antimuscarinic medication) without any OAB medication prescriptions/dispensings during all available observed baseline data.
Non-naïve new users	Patients with a new prescription/dispensing of an OAB medication (mirabegron or an antimuscarinic) who have a prescription/dispensing for some other OAB medication during all available observed baseline data.
Current exposure	*Current* exposure will include the days supply reported (or estimated) in the prescription/dispensing plus a grace period of 50% of the days supply of the most recent prescription/dispensing. The grace period accounts for variable adherence to medications where a patient may forget some scheduled doses and then still have some medication available beyond the days supply noted in the prescription
Recent exposure	*Recent* exposure will include the 60 days following the end of *current* exposure.
Past exposure	*Past* exposure will include all follow-up time after *recen*t exposure until censoring or a new prescription/dispensing of the same medication is observed.
MACE	Major adverse cardiovascular events (MACE): Defined as the first observed cardiovascular (CV) event, restricted to: acute myocardial infarction, stroke, CV mortality.

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4 SYNOPSIS

Date and Version # of Protocol Synopsis: **10 November 2016, Version 9.0**

Sponsor: **Astellas Pharma Global Development, Inc.**

Protocol Number ISN: 178-CL-114

EU PAS #: To be registered prior to data collection start

Name of Assessed Drug(s):

Mirabegron, Betmiga (EU), Myrbetriq (US)

Type of Study (refer to Global Definition STL-141):

Check One below:

☒ Mandated Study - US Food and Drug Administration

☐ Non-mandated Study

Check One below:

☐ Primary data collection

☒ Secondary data collection

☐ Mix of primary and secondary data collection

Check One below:

☒ Post-authorization safety study (PASS)

☐ Post-authorization efficacy study (PAES)

☐ Post-authorization study (PAS, non-PASS and non-PAES)

☐ *Other

**Note: "Other" category refers to non-interventional studies that do not explicitly mention any Astellas product in the title, objectives or inclusion criteria.* e.*g., a study to investigate natural course of a disease history or treatment pathways might fit in this category.*

Title of Study:

Post-authorization Safety Study
Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder

Guide to FDA and EMA reviewers

This amended protocol (version number 9.0) addresses key requests arising from discussion with the FDA during the Mirabegron post marketing requirement/post approval safety study (PMR/PASS) Type C meeting held on 21 March 2016, and the associated Meeting Minutes issued to Astellas on 05 April 2016. The following themes are addressed:

1. The protocol has been reformatted using the most recent version of the European Medicines Agency (EMA) template for consistency across the 178-CL-113 and -114 common Core protocols and site-specific protocols (in response to: FDA Type C Meeting Minutes issued to Astellas on 05 April 2016, page 4, General Comments related to the Core Study Protocols, comment #7) .
2. For the final report, rather than rely on algorithms for outcome identification in the Optum Research Database (ORD), Humana and Clinical Practice Research Datalink (CPRD)-unlinked, adjudication/validation will be completed, when permissions allow (in response to: FDA Type C Meeting Minutes issued to Astellas on 05 April 2016, page 6, FDA Response to Question 1b, comment #2).
3. A revised description of the interim report has been included. For all sites, no comparisons of incidence rates or counts of outcomes by drug (antimuscarinic vs mirabegron) will be provided. Instead, the interim report will include data summaries from each of the 5 data sources that will include patient accrual counts and length of observed follow-up. Linked data sources (CPRD-linked, Danish National Databases, and Swedish National Databases) will provide information on the number of acute myocardial infarction (AMI) and stroke cases and deaths. The data summaries from the US data sources (ORD and Humana) will also provide information on the estimated number of AMI and stroke events based on algorithms, the number of charts requested, and number of charts obtained; neither deaths nor adjudication status (i.e., confirmed case and non-case status) will not be reported. The data summary for the CPRD data will include the number of potential AMI, stroke, and deaths identified, as well as the number of physician surveys sought and obtained. The report will include a reassessment of power based on projected number of cases and person-time (in response to: FDA Type C Meeting Minutes issued to Astellas on 05 April 2016, page 9, Discussion to FDA Response to Questions 2a and 2b).
4. The statistical methodology has changed from using incidence rate ratios to hazard ratios to better accommodate the modeling procedures and allow for graphical review of the consistency of the hazard rates over time through the use of Kaplan Meier curves.

5. An assessment of the consequences of the loss of access to the Danish general practitioner database (DAMD) has been included (Section 9.4.3) (in response to: FDA Type C Meeting Minutes issued to Astellas on 05 April 2016, page 3, General Comments related to the Core Study Protocols, comment #1).
6. Measurement and selection of covariates (i.e., use of proxies and bias analysis) is described (Section 9.3.2) (in response to: FDA Type C Meeting Minutes issued to Astellas on 05 April 2016, page 3, General Comments related to the Core Study Protocols, comments #2 and #3).
7. A more extensive description of methods for conducting propensity score (PS) estimation and matching, and meta- analyses, has been included (Section 9.7.2) (in response to: FDA Type C Meeting Minutes issued to Astellas on 05 April 2016, page 4, General Comments related to the Core Study Protocols, comment #5).
8. Methods to assess the generalizability results across databases have been added (in response to: FDA Type C Meeting Minutes issued to Astellas on 05 April 2016, page 5, FDA Response to Question 1a, comment #3).

Study Rationale and Background:

Mirabegron is a beta 3-adrenergic receptor agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency, with a recommended starting dosage of 25 mg or 50 mg once daily, depending on country of use. During the clinical program, mirabegron administered at 50 mg once daily was associated with an increase in pulse rate of approximately 1 beat per minute compared with placebo and a mean of 0.4 to 0.6 mm Hg change from baseline systolic blood pressure/diastolic blood pressure compared with placebo in patients with OAB. These effects were mentioned as such in the European Union (EU) Risk Management Plan for mirabegron presented by Astellas in August 2011. The EMA requested a PASS to address the cardiovascular (CV) safety of mirabegron, with a special focus on elderly patients (day 120 comments from the Committee for Medicinal Products for Human Use). This PASS (or PMR in the United States [US]) is designed to address these concerns. The US Food and Drug Administration (FDA) has also requested a PMR study to evaluate CV safety in users of mirabegron. This protocol will be implemented to satisfy both the EMA and the FDA requests.

This PASS (or PMR in the US) is designed to generate additional evidence to help evaluate the results observed in the clinical trials. To implement the program, data sources were selected from 5 research centers. The investigators are from RTI Health Solutions (RTI-HS), Optum, Clinical Pharmacology and Pharmacy at the University of Southern Denmark (SDU), Centre for Pharmacoepidemiology (CPE) at Karolinska Institute (KI), and Comprehensive Health Insights (CHI).

The study population will include patients observed in each of the 5 databases, providing a wide array of patient characteristics, drug utilization, and medical practice patterns, which will enhance the generalizability of the study findings to the population of mirabegron users in real world practice, beyond clinical trials. In preparation for the conduct of this Core protocol (178-CL-114), database-specific validation studies were done to validate outcome definitions and assess the suitability of each data source for the PASS.[a] No clear and consistent trends in incidence rate ratios (IRRs) representing an increased risk of CV outcomes were observed across validation studies for any OAB medication, both overall and when restricting to age 65+ years, when comparing *current* exposure to each OAB drug with either *current* exposure to all other OAB drugs combined or *current* exposure to tolterodine (EU studies only). In the United Kingdom (UK) study, current use of oxybutynin was found to be associated with elevated point estimates of several CV outcomes, though statistically significant increases in IRRs were generally modest in magnitude (i.e., IRR $\leq$ 1.5). In addition to age and gender adjusted/standardized estimates, multivariate adjusted PS stratified models also failed to produce results suggesting a consistently increased risk of any CV outcome with any OAB medication across databases. Differences were noted in the performance of validation algorithms across databases.[1]

Planned Study Period:

Overall, the study period includes October 2012 (first observed use of mirabegron within the study data) through June 2019 (submission of final study report). Dates of data extraction and patient accrual start and end dates will vary by data source depending on availability and approvals.

Study Objectives:

The primary objectives of this study are:

- To estimate and compare the incidence of CV outcomes within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to antimuscarinic medications (as a group) used in the treatment of OAB. Outcomes include AMI, stroke, CV mortality, all-cause mortality and a composite measure of major adverse cardiovascular events (MACE), defined as the first of AMI, stroke, or CV mortality.
- To estimate the effect above among patients ages 65 years and older.
- To estimate the effect above among patients at high risk for CV events.
- To estimate the effect above among naïve new users and non-naïve new users of mirabegron or antimuscarinic medications.

The secondary objectives of this study are:

- To estimate and compare the incidence of CV outcomes within *current* exposure to mirabegron and *current* exposure to antimuscarinic medications (as a group) in

[a] Protocols 178-CL-115, 178-CL-116, 178-CL-118, 178-CL-119, 178-CL-130

intervals of time since initiation (i.e., < 60 days, 60 to < 120 days, 120 to < 180 days, >= 180 days).

- To estimate and compare the incidence of CV outcomes within categories of recency of use:
    - *recent* exposure to mirabegron vs *past* mirabegron exposure.
    - *current* exposure to mirabegron vs *past* mirabegron exposure.
    - *recent* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group).
    - *current* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group).
- To estimate and compare the effect of cumulative dose across tertiles (*current* exposure only) of mirabegron dose.
- To estimate and compare the effect of cumulative dose across tertiles (*current* exposure only) of antimuscarinic medication dose, restricted to the most commonly observed medication in each data source.
- To estimate and compare the incidence of CV outcomes within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to each *individual* antimuscarinic medication (where sample size allows).

Data Sources:

This will be a cohort study using data sources from 5 research centers. Throughout this document, the research centers and corresponding data sources will be described in the order in which they joined the PASS program. The initial investigators were from RTI-HS and Optum, later joined by investigators from the SDU, KI, and CHI.

Investigators from RTI-HS will lead the work involving the Clinical Practice Research Data Link (CPRD) databases. Based on data from the UK, the CPRD contains prescriptions issued by the general practitioner (GP) and the medical information recorded by GPs as part of their routine clinical practice, in addition to linkage to certain other data sources. Investigators from Optum in the US will lead the work involving the Optum Research Database (ORD), which contains medical and pharmacy claims with enrollment information covering the period from 1993 to the present for commercially insured patients, including members enrolled in Optum's Medicare Advantage and Part D program. Investigators from SDU will lead the work involving data from the Danish National Databases, including the Danish National Patient Register (DNPR), which provides data on all admissions to hospitals, the Danish National Prescription Database, and the Danish Registry of Causes of Death (DRCD). Investigators from the KI will lead work involving Swedish National Databases. Data will be obtained from the Total Population Register (with immigrations and emigrations), the National Patient Register (NPR, with inpatient and outpatient data), the Cause of Death Register (CDR), and the Swedish Prescribed Drug Register (PDR). Investigators from CHI will lead work involving a second US data source, the Humana Database. This database contains enrollment information linked to medical, laboratory, and pharmacy claims data for

Humana Medicare Advantage and commercially insured members across the US. A schematic of the 5 data sources is provided in Figure 1.

Analyses will include data summaries from each of the 5 databases. Linked data sources (CPRD-linked, Swedish Databases, and Danish Databases) will use information from their linked registries and cause of death registries to identify study outcomes. Outcomes identified through these linkages are considered valid and completed. However, due to FDA's concern about basing the final report on case-identification algorithms in unlinked data sources, study outcomes will be based on validated cases using physician surveys (CPRD-unlinked) and medical chart adjudication (ORD, Humana). Case-identification algorithms will be used to identify potential cases upon which medical record adjudication will be conducted.

The inclusion of all 5 databases will increase study power and enhance generalizability relative to a single database study by providing larger numbers of mirabegron-exposed patients and drawing data from a wider variety of users.

Study Population:

The study population will consist of episodes of person-time contributed during new user of medications used for the treatment of OAB. A new user of any drug of interest will be a patient who receives a prescription or dispensing for mirabegron or any antimuscarinic OAB drug during the study period without a prescription or dispensing for the same specific medication in the previous 12 months. At cohort entry, this definition permits a person to either be a naïve new user or a non-naïve new user.

Two study cohorts will be defined; 1 cohort will be comprised of person-time among new users of mirabegron, and 1 cohort will comprise person-time among new users of antimuscarinic medications used in the treatment of OAB, including oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine, as available in each data source. Patients who initiate both an antimuscarinic medication and mirabegron during the study period may contribute person-time to both drug cohorts. These patients may then have, for example, an outcome during *current* exposure to mirabegron which may also be considered as happening during *past* exposure to an antimuscarinic medication. For each patient, follow-up will start on the day following the first observed prescription for or dispensing of a drug of interest that meets the study entry criteria (Figure 2). Follow-up for each episode will end at the time of the earliest of the following: the end of the study period, death, disenrollment from the data source, end of the time period for which validated outcomes are available, or dispensing/prescription of non-tablet forms of antimuscarinic medications. For the analysis of *current* exposure, follow-up will end at the time of the earliest of any of the censoring criteria for study follow-up, or on the day when the days supply (plus grace period) has been reached.

Study Size / Number of Patients:

The study size will be determined by the uptake of mirabegron in the countries and population covered in the data sources at the time the study cohorts are created, and the period for which data is available in each population.

The following information on available numbers of mirabegron users is based on the data source-specific dates (Table 1) of the first observed dispensing or prescription. Through September 2015, there were 9,293 mirabegron initiators in the CPRD. Through June 2015, there were 9,951 mirabegron initiators in Optum's ORD database including commercially insured and Medicare Advantage enrollees. From 2013-2015, there were 23,829 mirabegron initiators in the Danish National Database. Data on counts of new initiators are not currently available for the Swedish National Database, but the number of mirabegron incident users was 8,116 in 2013, increasing to 21,445 prevalent and incident users in 2014, and 28,417 in 2015. Through June 2015, there were 3,475 mirabegron initiators in Humana's database including commercially insured and Medicare Advantage enrollees.

Study Design Overview:

This will be a cohort study comparing the incidence of CV outcomes (AMI, stroke, CV mortality, all-cause mortality and MACE) among new users of mirabegron and new users of any comparator antimuscarinic medication used in the treatment of OAB. To provide a sufficiently large patient population in order to evaluate the safety of mirabegron, the study will be conducted within multiple databases. Each of these populations will be studied according to the same Core protocol, although operational details will vary across sites due to the specifics of the data environments. In addition to data source-specific analyses, estimates obtained from all data sources will be analyzed using a meta-analysis approach for the final study report.

An independent external Scientific Advisory Board (SAB) has been installed to provide advice on the design, methodological, and analytical considerations for the mirabegron PASS/PMR protocol and corresponding common statistical analysis plan (SAP).

Inclusion/Exclusion Criteria:

The study population will consist of patient episodes and the contributed person-time among episodes of new user of mirabegron and episodes of new use of antimuscarinic medications. Database-specific protocols will outline the processes and codes used to identify the study medications.

Inclusion:

Patient episodes will be required to meet all of the following inclusion criteria, as ascertained from each of the automated data sources:

- Have a recorded prescription or dispensing for mirabegron or comparator antimuscarinic medication (oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine), with no dispensing or prescription for that specific medication in the prior 12 months (defined as the index prescription or dispensing).
- Be aged 18 years or older at the time of index prescription or dispensing of mirabegron or antimuscarinic medication.
- Have at least 12 months of continuous enrollment in the data source (thereby providing medical and dispensing/prescription history data, along with an operational

definition of new use) before the index prescription or dispensing of mirabegron or antimuscarinic medication.

Exclusion:

There are no exclusion criteria.

Comparative Groups:

Comparisons will be made between PS-matched episodes of mirabegron use and episodes of antimuscarinic medication use (as a group), with the exception of 1 secondary analysis that will compare episodes of mirabegron use to episodes of individual antimuscarinic medication use.

Patient Selection:

The predicted probability of starting treatment with mirabegron relative to antimuscarinic medications, conditional on baseline covariates, will be estimated to create a PS. The cohorts will then be formed by PS-matching at a ratio of 1 episode of mirabegron use to 1 comparator episode of antimuscarinic medication use.

Endpoints for Evaluation:

The primary outcomes of interest will be AMI (inclusive of fatal and non-fatal events), stroke (inclusive of fatal and non-fatal events), CV mortality (comprised of coronary heart disease (CHD) death and cerebrovascular disease death), and all-cause mortality. Based on the similar mechanisms and risk factors for the above outcomes, the composite outcome MACE— AMI, stroke, or CV mortality— will be examined. For potential cases identified in the UK and US data sources, study outcomes will be confirmed by obtaining and reviewing medical records, for the subsets of patients for whom permission to seek medical records is granted.

Independent Variables:

A range of characteristics will be evaluated for inclusion in the PS model, including demographics, characteristics that define elevated CV and mortality risk, relevant diagnoses related to OAB, health care utilization, and use of other medications in order to address confounding. The validation studies demonstrated that OAB drug use patterns varied within Europe and between Europe and the US; therefore, the selected confounders are likely to vary across data sources. When available, these characteristics will be obtained directly from within each data source. Otherwise, for variables not well characterized in the source data, proxies or estimates from external sources will be considered to estimate the potential effect of unmeasured confounding. Although only the 12-month period before cohort entry will be used to estimate rates of health care utilization, for most other covariates, all available information before the cohort entry date will be used (e.g., history of chronic obstructive pulmonary disease [COPD], menopause status).

Statistical Methods:

Sample Size Justification:

Sample size estimates are based on matching episodes of new use of mirabegron to episodes of new use of antimuscarinic medications with a 1:1 ratio. A cohort study with 75,000 episodes of patients currently exposed to mirabegron for 2.5 months and the same number of patients exposed to a comparison drug for the same length of time would be able to demonstrate an upper bound of the 95% confidence interval (CI) of the IRR lower than 1.5 when the true IRR is 1.00 with a probability of 80%. This estimate is based on the incidence of MACE events in clinical trials for mirabegron (583 per 100,000 person-years), which was observed in patients unexposed to mirabegron but taking a medication indicated for OAB in the clinical development program. It also assumes the average duration of use that was seen in several of the validation studies.

The sample size estimate based on hazard ratios (HRs) rather than IRRs is expected to be similar.

In the interim report, updated patient accrual and counts of cases will provide information for an updated estimate of the sample size for the final report.

Data Analysis:

Within each data source, patients' baseline characteristics will be determined through analysis of data available up to and including the cohort entry date. Baseline characteristics will include demographic variables including age and sex, comorbidities related to OAB and CV events, and specific medication and health care services use. Accounting for potential confounders will be performed by matching on a PS estimated from available covariates to balance cohorts with respect to those covariates. The list of potential confounding variables in each data source will be based on the availability of that covariate in the data source and will be provided in database-specific protocols. Cox proportional hazards regression models of the time from the day after cohort entry until the occurrence of an event or censoring will be built. Study results will be expressed as estimated adjusted HRs of the study outcomes along with CIs. For the primary objectives, the antimuscarinic medication initiators will comprise the comparator group, so the HR will express the relative risk of events among current mirabegron exposure to current antimuscarinic exposure.

A series of primary and secondary analyses will be done within each database and then meta-analyses will be performed pooled at an aggregate level across databases. Estimates based on overall matched patient episodes will be reported as well as estimates based on subsets of episodes from patients aged 65 years and older, patients at high risk for CV events, and by new user-status (naïve and non-naïve). Generalizability of study findings will be addressed by reporting medication use characteristics across exposure groups and by HRs, among the matched cohorts within planned strata (age and sex), along with available information on potential effect modifiers such as smoking.

Safety:

With the exception of demographic, drug utilization and length of follow-up descriptive analyses, most of the analyses described below are safety-related.

Interim Analyses:

The interim report will include data summaries from each of the 5 data sources that will include patient accrual counts and length of observed follow-up. Linked data sources (CPRD-linked, Danish National Databases, and Swedish National Databases) will provide information on the number of AMI and stroke cases and deaths. The data summaries from the US data sources (ORD and Humana) will include patient accrual counts and length of observed follow-up and also provide the estimated number of AMI and stroke events based on algorithms, the number of charts requested for outcome confirmation, and the number of charts obtained; adjudication status will not be reported (i.e., confirmed case and non-case status). The data summary for the CPRD will include the number of potential outcomes identified and the number of physician surveys to be obtained sought and obtained. For all sites, no comparisons of incidence rates or counts of outcomes by drug (antimuscarinic vs mirabegron) will be provided. The report will include a reassessment of power based on projected number of cases and person-time.

Dissemination Plan:

The combined interim and final study reports will be submitted to the FDA and the EMA.

Study results will be published following the International Committee of Medical Journal Editors guidelines,[2] and communication in appropriate scientific venues, e.g., International Society for Pharmacoepidemiology conferences, will be considered.

The appropriate STROBE checklist[3] will be followed for study reporting.

4.1 Flow Charts

Figure 1 Study Design Overview

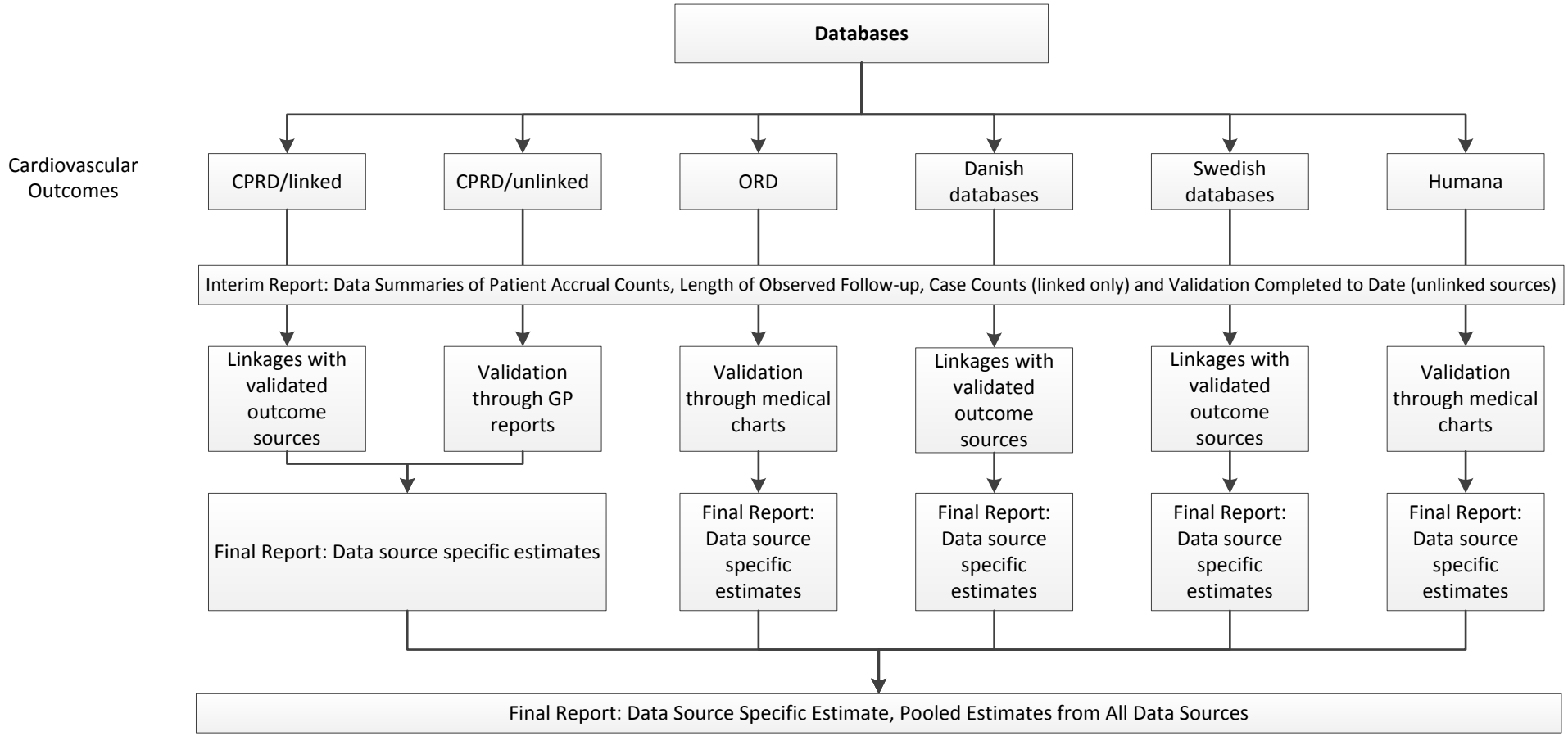
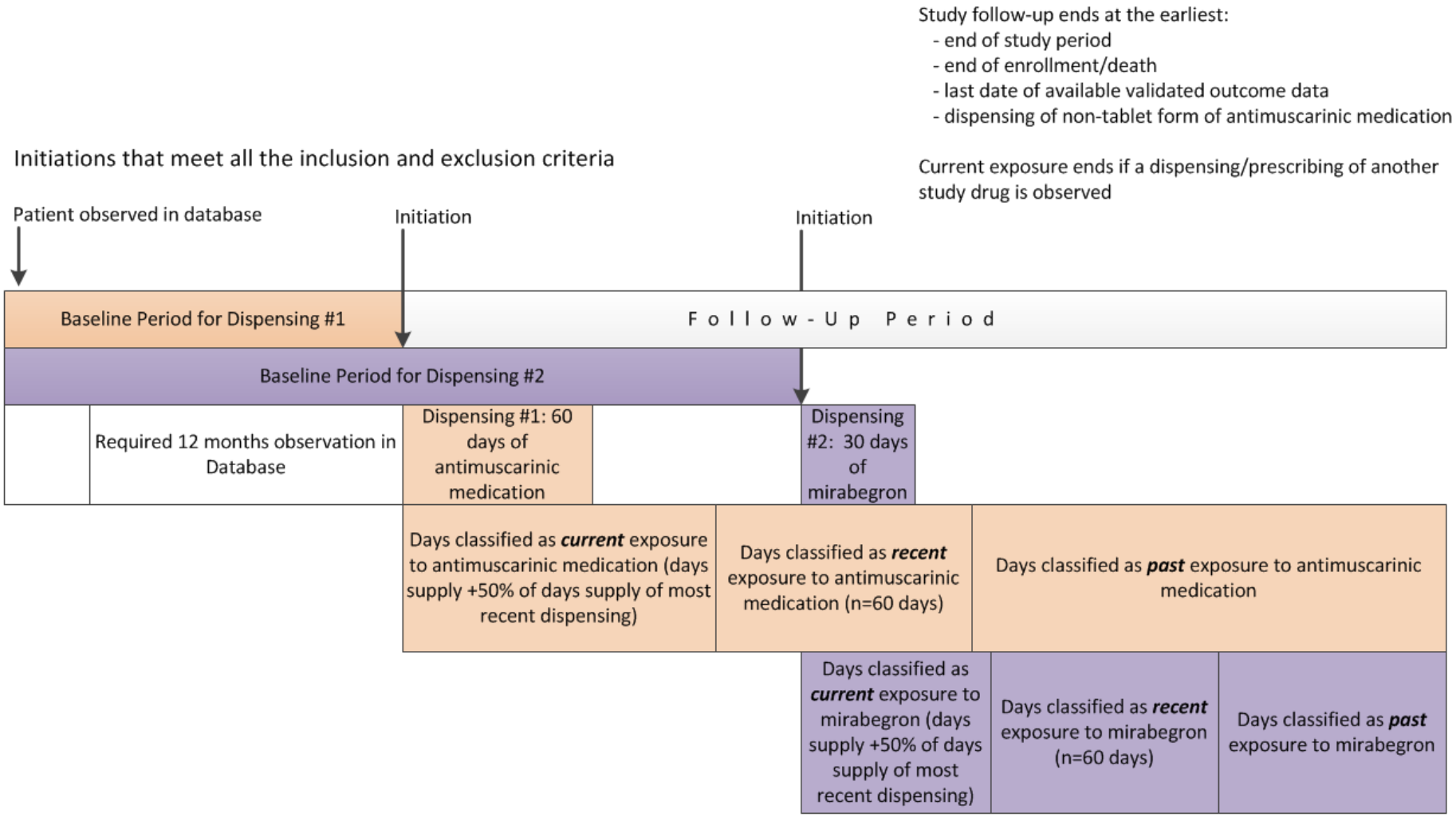


Figure 2 Schematic of Baseline and Follow-up Period



4.2 Schedule of Assessments

Table 1 Accrual Period for New Users for Interim and Final Report

	Dispensings/Prescriptions			Outcomes	
	Start	**Last Observed for Interim Report**	**Last Observed for Final Report**	**Last Observed for Interim Report**	**Last Observed for Final Report**
CPRD-linked	Feb 2013	2015/16	Dec 2016/2017	2015/16	Dec 2016/2017
CPRD-unlinked	Feb 2013	Nov 2017	Apr 2018	Nov 2017	Apr 2018
Optum	Oct 2012	Dec 2016	Dec 2017	Dec 2016	Dec 2017
Danish registers	Apr 2013	Dec 2017	Dec 2018	Dec 2017	Dec 2018
Swedish registers	May 2013	Dec 2015[a]	Dec 2016	Dec 2015[a]	Dec 2016
CHI-Humana	Oct 2012	Dec 2016	Dec 2017	Dec 2016	Dec 2017

[a] Dependent on timely delivery of requested registry data.

5 AMENDMENTS AND UPDATES

Please note that this protocol has been transferred to the most recent version of the EMA template per the request of the FDA to improve readability of submissions, reduce errors, and preference for a unified table of contents from multiple contractors (as per 21 March 2016 FDA Type C Meeting Minutes, issued to Astellas on 05 April 2016). Due to differences in the section contents between protocol versions, only major changes rather than detailing section-by-section modifications will be listed.

Table 2 Amendments and Updates to Protocol 178-CL-114

Number	Date	Section number of study protocol	Reason
1. For the final report, rather than rely on algorithms for outcome identification in the ORD, Humana and CPRD-unlinked, adjudication/ validation will be completed, when permissions allow.	Nov 2016	Synopsis, Section 9.7.2	Implemented after recommendations made during the 21 March 2016 FDA Type C meeting, in response to: FDA Type C Meeting Minutes issued to Astellas on 04/05/2016, page 6, FDA Response to Question 1b, comment #2.
2. Methods for the meta-analysis have been revised and now conform with standard software to pool estimates across published studies.	Nov 2016	Synopsis, Section 9.7.2	Research Partners discussed methodology and available software for performing meta-analysis and concluded this approach is preferred because it is standardized, generalizable and replicable.
3. Separate descriptions of the CPRD-linked and CPRD-unlinked data have been provided.	Nov 2016	Synopsis, Section 9.4.1	Implemented after recommendations made during the 21 March 2016 FDA Type C meeting, in response to: FDA Type C Meeting Minutes issued to Astellas on 04/05/2016, page 7, FDA Response to Question 1b, comment #3.
4. The statistical methodology has changed from using incidence rate ratios to hazard ratios.	Nov 2016	Synopsis, Section 9.7.2	Research Partners discussed methodology and preferred this approach to better accommodate the modeling procedures and allow for graphical review of the consistency of the hazard rates over time through the use of Kaplan Meier curves.
5. Sample size estimates have been revised	Nov 2016	Synopsis Section 9.7.1	Updated estimates of patient accrual were taken into consideration.
6. The effect of cumulative dose will be examined only within tertiles of mirabegron and separately within tertiles of antimuscarinic medication (most commonly observed in each data source) rather than by comparing across tertiles of mirabegron vs antimuscarinic medications.	Nov 2016	Synopsis Section 8	This change was made by the Research Partners after additional consideration of the most relevant comparisons given the observed differences in individual antimuscarinic medication use across data sources.

6 MILESTONES

Table 3 Milestones for Development and Conduct of Protocol 178-CL-114

Milestone	Planned Periods
Registration in the EU PAS register	TBD
Protocol submission to FDA	July 2014
Start of data collection (final report) *	CPRD - Quarter 1, 2018 ORD – October 2016 Danish National Databases – June 2016 Swedish National Databases – December 2016 Humana – October 2016
End of data collection (final report)**	CPRD - Quarter 1, 2019 ORD – April 2019 Danish National Databases – January 2019 Swedish National Databases – March 2017 Humana – April 2019
Summary report submission for the US and EU validation studies	March 2015
Revised protocol submission to FDA	November 2016
Statistical analysis plan (SAP) submission to FDA	November 2016
Site specific protocols to FDA	January 2017
Interim report submission to FDA	June 2018
Final report of study results	June 2019
* In the case of secondary use of data, the date from which data extraction starts. Due to differences in data access, some sites will pull data in a series, while other sites will do 1 large data pull when accrual is complete.	
** In the case of secondary use of data, the date from which the analytical dataset is completely available.	

7 RATIONALE AND BACKGROUND

Mirabegron is a beta 3-adrenergic receptor agonist indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency, with a recommended starting dosage of 25 mg or 50 mg once daily.

During the clinical program, mirabegron administered at the dose of 50 mg once daily was associated with an increase in pulse rate of approximately 1 beat per minute compared with placebo and a mean of 0.4 to 0.6 mm Hg change from baseline systolic blood pressure/diastolic blood pressure compared with placebo in patients with OAB. These effects were mentioned as such in the EU Risk Management Plan for mirabegron presented by Astellas in August 2011 and were considered potential risks by the FDA that merited further consideration in a real-world setting. The EMA requested a PASS study to address the CV safety of mirabegron, with a special focus on elderly patients (day 120 comments from the Committee for Medicinal Products for Human Use). An outline of this research program was submitted to the EMA and was included in the new drug application documentation submitted to the FDA in May 2012.

Based on review by a blinded, external Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron, the proportion of patients with at least 1 adjudication-confirmed CV event was 0.4% (placebo), 0.3% (total mirabegron), and 0.3% (tolterodine) in the global OAB 12-week phase 2/3 population, and total mirabegron (0.9%) and tolterodine (1.4%) in the European/North American long-term controlled population. Using the global OAB 12-week phase 2/3 population, the relative risk (RR) for the occurrence of Antiplatelet Trialists' Collaboration events or MACE was 0.24 (95% CI: 0.02, 1.69) for patients receiving mirabegron compared with placebo.[4] Data in the public domain about the association between OAB medications and CV concerns are scarce. In a study of US patients performed in the HealthCore Integrated Research Database and the GE Healthcare Database, baseline CV comorbidity was higher in the OAB group — patients with a diagnosis of OAB or who were treated with OAB antimuscarinic drugs — (39%) than in age- and sex-matched patients without either an OAB diagnosis or exposure to OAB antimuscarinic drugs (21%).[5] CV comorbidities with higher prevalence in the OAB group included hypertension, diabetes, ischemic heart disease, and conduction disorders. In addition, the prevalence of use of non-OAB drugs with antimuscarinic effects was also higher in the OAB group (33% vs 17%). Comparing OAB patients treated with OAB antimuscarinic drugs and age- and sex-matched OAB patients with no such treatment, CV comorbidity had similar prevalence (39% vs 38%). Use of non-OAB drugs with antimuscarinic effects was higher among treated OAB patients than among the untreated OAB patients (37% vs 29%).

A related US-based study performed in the GE Healthcare Database found that OAB patients treated with OAB antimuscarinic drugs had baseline heart rate distributions similar to those with no such treatment.[4,5] In this study, treated OAB patients had a higher proportion of CV comorbidity (59%) than untreated OAB patients (54%), including a higher proportion of hypertension, diabetes, and cerebrovascular disease. However, age and sex, 2 key risk factors for CV conditions were not balanced among the treated and untreated OAB patients (median

age: 66 vs 59 years; male sex: 17% vs 14% in treated vs untreated OAB patients, respectively). None of the studies provided information on the profiles of users of individual antimuscarinic drugs.

Some studies on drug utilization have been identified, and key findings are summarized below as they are of relevance for the program design. In a drug utilization study that used electronic medical records from the general population in the UK, adult female users of OAB drugs had a mean age of 63.9 years.[6] This study was conducted in The Health Improvement Network (THIN) database, which partially overlaps with the CPRD in terms of contributing practices. In this study, the mean time from diagnosis to first drug treatment was 28.7 months, and the mean (standard deviation) number of treatment episodes per patient was 1.65 (1.31). Of all study patients, 11% had more than 3 treatment episodes during follow-up. Overall drug discontinuation at 6 months was 58.8%, although it varied by drug: 53% for solifenacin and 89% for terodiline (an OAB medication withdrawn for cardiotoxicity). At 12 months, overall drug discontinuation was 77.2%, lowest for tolterodine extended release (76%) and highest for terodiline (99%). Switching occurred in 15.8% of the treatment episodes.

In a study using reimbursed prescriptions from Odense, Denmark, 66.2% of the individuals prescribed OAB drugs were women (mean age, 68.0 years) and 33.8% were men (mean age, 69.0 years).[7] All drugs had discontinuation rates over 50% at 6 months and over 75% at 12 months, with the exception of trospium chloride, which had a discontinuation rate of 64% at 12 months.

In a drug utilization study in the US that used claims data from a managed care health plan, 53.7% of adult new users of tolterodine or oxybutynin (rapid- or slow-release formulations) had a code for OAB, 81.6% were women, and the mean (standard deviation) age was 55.7 (14.5) years.[8] Of these, 44.5% did not refill the initial prescription, 86.8% had discontinued the initial treatment at 12 months after the first prescription, and 13.3% of study drug users switched to another formulation or drug.

In preparation for the conduct of this Core protocol (178-CL-114), a series[*] of studies was done in each of the data sources to validate outcome definitions and to assess the suitability of each data source for the post authorization safety program. Because mirabegron was not yet available, these studies were completed using only antimuscarinic medications.

No clear and consistent trends in IRRs representing an increased risk of CV outcomes were observed across validation studies for any OAB medication, both overall and when stratifying by age 65+ years, when comparing *current* exposure to each OAB drug with either *current* exposure to all other OAB drugs combined or *current* exposure to tolterodine (EU studies only). In the UK study, current use of oxybutynin was found to be associated with elevated point estimates of several CV outcomes, though statistically significant increases in

[*] Protocols 178-CL-115, 178-CL-116, 178-CL-118, 178-CL-119, 178-CL-130

IRRs were generally modest in magnitude (i.e., IRR ≤ 1.5). In addition to age and sex adjusted/standardized estimates, multivariate adjusted and PS stratified models produced results suggesting there was not a consistently increased risk of any CV outcome with any OAB medication across databases. Differences were noted in the performance of validation algorithms across databases.

8 RESEARCH QUESTION AND OBJECTIVES

The primary objectives of this study are:

- To estimate and compare the incidence of CV outcomes within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to antimuscarinic medications (as a group) used in the treatment of OAB. Outcomes include AMI, stroke, CV mortality, all-cause mortality and a composite measure of MACE, defined as the first of AMI, stroke, or CV mortality.
- To estimate the effect above among patients ages 65 years and older.
- To estimate the effect above among patients at high risk for CV events.
- To estimate the effect above among naïve new users and non-naïve new users of mirabegron or antimuscarinic medications.

The secondary objectives of this study are:

- To estimate and compare the incidence of CV outcomes within *current* exposure to mirabegron and *current* exposure to antimuscarinic medications (as a group) in intervals of time since initiation (i.e., < 60 days, 60 to < 120 days, 120 to < 180 days, >= 180 days).
- To estimate and compare the incidence of CV outcomes within categories of recency of use:
  - *recent* exposure to mirabegron vs *past* mirabegron exposure.
  - *current* exposure to mirabegron vs *past* mirabegron exposure.
  - *recent* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group).
  - *current* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group).
- To estimate and compare the effect of cumulative dose across tertiles (*current* exposure only) of mirabegron dose.
- To estimate and compare the effect of cumulative dose across tertiles (*current* exposure only) of antimuscarinic medication dose, restricted to the most commonly observed medication in each data source.
- To estimate and compare the incidence of CV outcomes within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to each *individual* antimuscarinic medication (where sample size allows).

9 RESEARCH METHODS

In the Core study, cohorts of patients who receive drugs used in the treatment of OAB will be identified from the US and European populations. The new-user design for the study medications will be adopted. Switching among the antimuscarinic medications may occur among patients with OAB, and the validation studies suggest that the patient characteristics of initiators of each of the antimuscarinic medications are quite similar (with little evidence of channeling among antimuscarinic medication). Nevertheless, the approach in this study is to select a comparison cohort comprised of a combination of new users of any antimuscarinic medication and will include additional analyses of comparisons of mirabegron to individual antimuscarinic medications. The person-time contributed by the new users of antimuscarinic medications (alone or as a group) will provide an estimate of the "background" incidence of the CV outcomes in the study population.

9.1 Study Design

This is a cohort study including patients exposed to mirabegron or antimuscarinic medications. Exposure will be based on prescription/dispensing data and only new users will be included. Patients may switch between antimuscarinic medications and mirabegron, and therefore, the analysis will be episode-of-use level, rather than patient-level. Each mirabegron use episode will be matched to 1 antimuscarinic medication use episode by data source and year-specific PSs.

9.1.1 Endpoints

Each of the following individual study outcomes will be evaluated:

- AMI (inclusive of fatal and non-fatal events)
- Stroke (inclusive of fatal and non-fatal events)
- CV mortality, comprised of:
  - CHD mortality
  - Cerebrovascular disease mortality
- All-cause mortality

Because the CV outcomes have similar mechanisms and risk factors, the composite MACE outcome - AMI, stroke, or CV mortality - will also be examined.

All-cause mortality is included as an outcome to captures deaths that are not correctly categorized as CV-related.

Clinical Definitions of Endpoints

Acute myocardial infarction: evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, including ST-elevation myocardial infarction (MI) and non–ST-elevation MI.[9,10]

Stroke: An acute stroke is defined as the rapid onset of a persistent neurological deficit attributed to an obstruction or rupture of the arterial system.[11] Patients with stroke can die before reaching the hospital; a complete assessment of acute stroke events requires the

identification of community stroke deaths. There are 2 subtypes of stroke, hemorrhagic and ischemic:

- Hemorrhagic stroke: Disease of abrupt onset that causes neurologic damage due to a hemorrhage into brain tissue (parenchymatous hemorrhage) or hemorrhage into the spaces surrounding the brain, most frequently the subarachnoid space.[12,13] Subdural and epidural hemorrhages are excluded from this definition.
- Ischemic stroke: Although older and traditional definitions were based on the duration of the neurological symptoms and the presence of cerebral cell death, the need for an early intervention with thrombolytic treatments and imaging (that can detect cell damage involving very small areas of the brain) have rendered those definitions obsolete. A universal definition of cerebral infarction as the presence of evidence of brain or retinal cell death due to cerebral ischemia will be used. [14,15,16]

CV mortality: death from CHD or cerebrovascular disease, as follows:

- CHD death: fatal episode of AMI or CHD death.
- Cerebrovascular disease death: fatal episode of stroke or cerebrovascular disease death.[17]
- Almost one third of the patients suffering an AMI die suddenly before arriving at the hospital, and the diagnosis cannot be completed (e.g., no electrocardiogram is obtained to show the typical changes or no autopsy is performed). For this reason, community (out-of-hospital) CHD deaths are included in the definition of AMI, when data are available. Because claims data do not include cause of death, this information will be obtained from the National Death Index (NDI) linkage for the Optum and Humana data sources.

MACE composite outcome: the first event of AMI, stroke, or CV death for each patient.

All-cause mortality: death due to any cause.

Endpoint Identification and Ascertainment

As described in more detail in the subsections below, outcomes will be identified and ascertained differently in the different data sources. Each research partner has conducted validation studies of CV outcomes in preparation for the Core protocols. Based on those findings and the implementation of International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification (ICD-10-CM) codes in the US health care system, some of the research partners will be using revised algorithms or seeking medical charts or physician surveys for case confirmation. In addition, linkage to death registry data will be used for ascertaining mortality and cause of death.

CPRD

In the CPRD, linkage with National Health Service (NHS) hospital episode statistics (HES) and Office for National Statistics (ONS) vital statistics is available for approximately 50% of the practices. In patients from these practices, AMI and stroke events will be identified from linkage with HES data, coded according to the ICD-10-CM. Cause of death, especially

important in patients who died out of the hospital, will be ascertained from ONS data; thus, out-of-hospital CHD deaths (included in the AMI outcome) and out-of-hospital cerebrovascular disease deaths (included in the stroke outcome) will be able to be identified. Deaths with codes for CHD recorded as an underlying cause of death in the ONS file and not linked to a hospitalization will be considered to be confirmed out-of-hospital CHD deaths. Any death occurring within 30 days after the hospital admission date for a hospitalization with a primary discharge diagnosis of AMI will be considered a fatal AMI case.

In data from the unlinked practices, AMI and stroke events will be identified based on all of the clinical elements present in the data source. Operational definitions, which reflect broadly accepted clinical definitions, will be implemented through a computerized algorithm. The operational definition for AMI includes aspects such as hospitalization, primary angioplasty, elective angioplasty, administration of thrombolytic therapy, abnormal results of cardiac enzyme measurements, electrocardiogram indicative of AMI, etc. For stroke, the operational definition includes thrombolytic therapy, embolization, residual neurologic damage, etc. Identified cases will also undergo clinical review through questionnaires sent to practicing physicians. Deaths during the study period will be identified using the date of death provided by the CPRD in the patient data set. The CPRD assigns the date of death by screening the electronic medical records for Read codes indicating death, using date of death recorded in the death administration structured data area of CPRD GOLD, and identifying patients who transferred out of the practice because of death. Cause of death will be identified from electronic data when available. A patient will be considered to have died from CHD when there is postmortem evidence of recent AMI, a recent coronary artery occlusion or antemortem evidence of CHD in the absence of another cause of death, or CHD recorded as the underlying cause of death. All cases of hospitalized AMI identified in the non-linkable practices with a code for death from any cause recorded by the GP within 30 days after the index date of the AMI will be considered fatal AMI cases. A patient will be considered to have died from cerebrovascular disease when there is postmortem evidence of recent stroke, a recent cerebral artery occlusion or antemortem evidence of stroke in the absence of another cause of death, or stroke recorded as the underlying cause of death. All cases of hospitalized stroke identified in the non-linkable practices with a code for death from any cause recorded by the GP within 30 days after the index date of the stroke will be considered fatal stroke cases.

ORD and Humana

Optum and CHI completed a detailed assessment of the validity of AMI and stroke algorithms within the commercially insured population of the ORD and Humana databases as part of the validation study. Based on FDA feedback, these 2 US sites will utilize previously published algorithms to identify potential cases and will seek medical charts for all potential cases identified. These medical records will be adjudicated with respect to case status, and adjudicated results will be used for the final analyses.

AMI and stroke outcomes will be identified from claims data and individual cases will be adjudicated via medical record review by a panel of physicians. Adjudicated results will be used for the outcome analyses.

Potential AMI cases will be identified based on the presence of an ICD-9-CM code for AMI (410.x0, 410.x1) in the principal (or primary) diagnosis position on at least 1 facility claim for hospitalization.[18] Claims from emergency departments will not be included in the case identification as they are likely to lead to misclassification. During the period of ICD-10-CM coding, potential AMI cases will be identified based on the presence of an ICD-10-CM diagnosis code for AMI (I21.xx or I22.xx) in the principal (or primary) diagnosis position on at least 1 facility claim for inpatient hospitalization.

Potential stroke cases will be defined by the presence of an ICD-9-CM code 430, 431, 433.x1, or 434.x1 in the principal (or primary) diagnosis position on at least 1 facility claim for hospitalization. This definition is similar to 1 described in Andrade, et al, [19] however does not include ICD-9 code 436 (*Acute, but ill-defined, cerebrovascular disease)*, per FDA request, because it contributed to the low positive predictive values (PPVs) observed in the ORD validation study.

During the period of ICD-10-CM coding (starting October 2015), potential stroke cases will be identified based on the presence of an ICD-10-CM diagnosis code for stroke (I60.xx, I61.xx, I63.xx, or I64.xx) in the principal (or primary) diagnosis position on at least 1 facility claim for inpatient hospitalization.

Mortality information from the Social Security Administration (SSA) Death Master files is routinely incorporated into the ORD. This file will allow evaluation of all-cause mortality as an outcome of interest upon receipt of necessary approvals; however, cause of death cannot be determined from this source. Cause-specific mortality, such as CV deaths, can be ascertained through the NDI Plus search, upon the receipt of necessary approvals.

For assessment of mortality outcomes and the MACE composite outcome, identification of all-cause and CV mortality among cohort members will be conducted via linkage to the NDI. In order to determine CV mortality, the NDI Plus, which contains cause of death codes, will be used. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year, so deaths after 2017 will not be captured.[*] Person-time at risk for death and for the MACE outcome will be censored at the time when NDI data are not available.

Danish National Databases

In Denmark, outcomes will be ascertained through the Danish National Patient Register (DNPR), which provides administrative and medical information on all admissions to Danish hospitals since 01 January 1977. From 1995 onwards, half-day patients, outpatients, and contacts to the emergency room were also captured. Diagnosis codes are registered by the

[*] This assumes that NDI data for 2016 will be available by early 2018 in time for incorporation in the final report.

discharging physician at the time of the hospital discharge. Hospital discharge diagnoses are currently coded using ICD-10 codes (ICD-8 until 1996). Data on surgical procedures are also recorded. From 1996, invasive therapeutic procedures (such as surgery and percutaneous interventions) have been coded according to the Nordic Medical Statistics Committees Classification of Surgical Procedures.

Hospitalization data are complete in the DNPR, except for psychiatric hospitalizations. The main discharge diagnosis will be used to identify AMI and stroke, since this code indicates the reason for the hospitalization episode. For stroke, imaging and/or surgical procedures (hemorrhagic stroke) in the hospital will also be used to ascertain acute events.

Table 4 ICD-10-CM Codes Indicating Acute Myocardial Infarction and Stroke

Code	Description
Acute myocardial infarction	
I21.-	Acute myocardial infarction
I22.-	Subsequent myocardial infarction
Stroke	
I60.-	Subarachnoid hemorrhage
I61.-	Intracerebral hemorrhage
I63.-	Cerebral infarction
I64	Stroke, not specified as hemorrhage or infarction

ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification.*

ICD-10 codes have been shown to have good PPVs for the outcomes of interest, 82%-100% for AMI and 79%-94% for stroke. Validated ICD-10 codes for AMI and stroke, and published results of validation studies, are presented in Annex 5.

Cause-of-death data are available through the cause of death registry and will be used to determine the cause of death of patients who died before reaching the hospital.

Swedish National Databases

In Sweden, CV outcomes will be identified through the Swedish NPR, which currently covers more than 99% of all somatic (including surgery) and psychiatric hospital inpatient and outpatient visits. Since 2001, the register also contains all outpatient visits including day surgery and psychiatric care from both private and public caregivers. Primary care is not yet covered in the NPR. Hospital diagnoses are coded using ICD-10 codes. As in the Danish National Databases, the main discharge diagnosis will be used to identify AMI and stroke events. Since 1997, a Swedish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures has been in use. Current procedures are listed in the Nordic Classification of Surgical and Medical Procedures. Cause-of-death data are available through the CDR and will be used to determine the cause of death of patients who died before reaching the hospital.

Several validation studies of diagnoses in the NPR have demonstrated good PPVs for AMI and stroke. Validated ICD-10 codes for AMI and stroke and published results of validation studies are presented in Annex 6.

9.1.2 Comparative Groups

The probability of starting treatment with mirabegron relative to antimuscarinic medications, conditional on baseline covariates, will be estimated to create a PS. For all analyses, the comparisons will be made between PS-matched episodes of mirabegron use and episodes of antimuscarinic medications use. Methods for matching are described in Section 9.7.2.

9.2 Setting

This will be a cohort study using data sources from 5 research centers. The study population will include eligible patients observed in each of the 5 databases, providing a wide array of patient characteristics, drug utilization and medical practices patterns.

Investigators from RTI-HS will lead the work involving the CPRD databases. Based on data from the UK, the CPRD contains prescriptions issued by the GP and the medical information recorded by GPs as part of their routine clinical practice, in addition to linkage to certain other data sources. The CPRD has approximately 5.1 million active patients. Patients are representative of the whole UK population in terms of age and sex. For a large subset of practices in England (herein "CPRD-linked"), these data are linkable with hospitalization records and national mortality data. For the non-linkable practices (herein "CPRD-unlinked"), CV cases can only be identified through automated medical records and validated by additional information obtained from GPs.

Investigators from Optum Epidemiology in the US will lead the work involving the ORD, which contains medical and pharmacy claims with enrollment information covering the period from 1993 to the present. The underlying population is geographically diverse across the US. The ORD includes complete medical and pharmacy information for commercially insured members, as well as for Medicare enrollees with medical and Part D (prescription) coverage. Pharmacy claims contain sufficient information to trace patients' pharmacy expenditures through the multiple phases of the Part D plans. Claims data in the ORD can be linked to the SSA Death Master File to ascertain date of death among health plan members who are lost to follow-up. Additional linkages to the NDI for cause-of-death information may be sought. For a subset of cases, CV outcomes can be validated by obtaining additional information from medical records.

Investigators from the Clinical Pharmacology and Pharmacy at SDU will lead the work involving Danish data. In Denmark, the Danish health care system provides universal coverage to all Danish residents, approximately 5.6 million individuals in 2013. The centralized Civil Registration System in Denmark allows for personal identification of the entire Danish population through a unique identification number (Central Person Registry [CPR] number). Use of CPR numbers ensures unambiguous record linkage between all Danish registries, such as the DNPR, which provides data on all admissions to hospitals, the Danish National Prescription Database and the Danish Registry of Causes of Death.

Investigators from the CPE, KI will lead work involving Swedish data. In Sweden, all residents are entitled to publicly financed health care covering the entire population, estimated to be 9.64 million in 2013. Many population-based health registries have been

established with the use of the unique personal registration number. The personal registration number is given at birth or immigration to all Swedish residents and kept throughout life. In health care, the personal registration number is used for vital statistics and is also the unique identifier and key variable linking different registers. Information in the registers is recorded by current ICD, ICD-O/3, Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) and/or Anatomical Therapeutic Chemical (ATC) codes. Data will be obtained from the Total Population Register (with immigrations and emigrations), the National Patient Register (with inpatient and outpatient data), the CDR and the Swedish PDR.

Investigators from CHI will lead work involving a second US data source, the Humana Database. This database contains enrollment information linked to medical, laboratory, and pharmacy claims data for Humana Medicare Advantage and commercially insured members across the US (~14.2 million total current Humana members as of September 2015). The Medicare population over 65 years of age represents the majority of the enrolled population at Humana. The Humana Database available for research covers the time period from 2007 to present, and similar to the ORD, CV outcomes can also be validated through medical record review.

9.2.1 Selection of Study Population

The study population will consist of males and females at least 18 years old at initiation who are new users of medications used for the treatment of OAB. A new user of any drug of interest will be a patient who receives a prescription or dispensing for mirabegron or any antimuscarinic OAB drug during the study period without a prescription or dispensing for the same specific medication in the previous 12 months. As the study is focusing on the evaluation of the safety of mirabegron relative to antimuscarinic medications, the study population will include all new users of mirabegron and all new users of antimuscarinic medications; an OAB diagnosis will not be required. Due to differences in the medication coding schemes used in the various databases involved in the study, the site-specific protocols will outline the codes used to identify the study medications in each database.

9.2.2 Inclusion

The study will include treatment episodes from males and females. The patient episodes in the study will be required to meet all of the following inclusion criteria as ascertained from each of the automated data sources:

- Have a recorded prescription or dispensing for mirabegron or comparator antimuscarinic medication (oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine), with no dispensing or prescription for that specific medication in the prior 12 months before cohort entry (defined as the index prescription or dispensing). The index prescription will be considered the first treatment episode; once a patient enters the cohort (mirabegron or antimuscarinic medications [as a group]), a patient may switch between individual antimuscarinic medications and mirabegron.

- Be aged 18 years or older at the time of index prescription or dispensing of mirabegron or antimuscarinic medication.
- Have at least 12 months of continuous enrollment in the data source (thereby providing medical and dispensing/prescription history data, along with an operational definition of new use) before the index prescription or dispensing of mirabegron or antimuscarinic medication.

9.2.3 Exclusion

There are no exclusion criteria.

9.2.4 Discontinuation Criteria (Treatment Episode Censoring Criteria)

Follow-up of eligible patient treatment episodes will start on the day after the index prescription or dispensing for mirabegron or antimuscarinic medication (first treatment episode). There are two types of discontinuation (censoring) criteria for this study, including the end of an exposure episode and censoring of study follow-up.

Within each patient treatment episode, follow-up for each study outcome will finish at the earliest of the following dates:

- Occurrence of the individual study endpoint (counted separately for each endpoint within episodes).
- End of the study period.
- Last date of data with validated CV outcomes (or death) within each of the data sources.
- Disenrollment from the data source (e.g., emigration, death).
- Dispensing or prescription of non-tablet types of antimuscarinic medication (due to the difficulty assigning exposure-time during use of syrups, patches, gels, or intravesical medications).
- Dispensing or prescription of mirabegron and an antimuscarinic medication on the same day, or dispensing or prescription of two antimuscarinic medications on the same day.

Throughout the study period, patients will be eligible to contribute additional initiation episodes until the earliest of the following dates:

- End of the study period.
- Last date of data with validated CV outcomes (or death) within each of the data sources.
- Disenrollment from the data source (e.g., emigration, death).

For the composite MACE outcome, person-time follow-up will terminate at the date of occurrence of the first targeted CV event within an episode. In contrast, person-time for a specific outcome will stop accruing at the occurrence of that outcome (i.e., only the first event of each type of outcome within an episode will be counted in the incidence rates). Patients may experience multiple types of events, therefore, even after a patient

experiences 1 of the CV events, person-time of follow-up will continue to accumulate until the date of occurrence of any different CV event or end of follow-up.

9.3 Variables

9.3.1 Exposure Definition and Measurement

Each day of exposed person-time will be classified into mutually exclusive categories based on specific drug use and recency of use (current, recent, and past use to a mirabegron as well as current, recent, and past use antimuscarinic medication [as a group]). In addition, *current* exposure to individual antimuscarinic medications will be defined for additional examination relative to mirabegron exposure. Patients will contribute person-time to different exposure categories if they switch or discontinue treatment. Days supply will be used to define recency of use and methods to define days of use will be described in site-specific protocols. For all databases, *current* exposure will include the days supply reported (or estimated) in the prescription/dispensing plus a grace period of 50% of the days supply of the most recent prescription/dispensing. The grace period accounts for variable adherence to medications where a patient may forget some scheduled doses and then still have some medication available beyond the days supply noted in the prescription. *Recent* exposure will include the first 60 days after *current* exposure, and *past* exposure will include person-time after the 60 days of *recent* exposure until the end of study follow-up or a new prescription/dispensing of the same medication is observed. It is assumed that any CV effects of OAB medications will present shortly after first use and continue while patients continue to use the medication, and that the effects will decline after the medication is discontinued. The range of days supply (e.g., 30, 90, 120 days) is likely to vary within and between data sources. Descriptive information on the days supply will be provided. If there are extreme values, data source specific sensitivity analyses restricting to the more common days supply episodes will be performed.

This study is based on the assumption that it will be uncommon for patients to have concurrent use of multiple OAB drugs (although therapy episodes built from prescription data may overlap during the transition between treatments), exposure to the first drug will be considered stopped at the time of a dispensing of an additional OAB drug for the purpose of classifying recency of use. It may be that in actual practice, physicians prescribe mirabegron along with an antimuscarinic medication. This exposure will not be evaluated in this study.

Exposure to each study drug will be defined according to the days supply of each prescription. Days of supply will be ascertained from the prescription or dispensing information recorded in the data sources. In data sources without direct information on days supply, this variable will be estimated from the results of descriptive analysis of the time between consecutive prescriptions, or from the defined daily dose (DDD) (for example, in the Danish Registry of Medicinal Product Statistics and in the Swedish PDR). If missing values are found in the dose field, the dose will be estimated from descriptive analysis of the available recorded information (strength, number of units, amount of drug prescribed, etc.).

The cumulative dose of mirabegron and dose of antimuscarinic medications will be defined separately, according to database- specific definitions of days supply, ascertained from the prescription or dispensing information recorded in the data sources and the tablet strength. Methods for the calculation will be outlined in the common Core SAP and site-specific protocols. Briefly, cumulative dose will be based on days supply (or estimate of days supply) and strength of the tablets. No grace period will be factored in for the calculation of cumulative dose. For each patient, dose will be summed across all matched episodes of use (matching will be described in Section 9.7.2). The cumulative value on the last day of *current* exposure will be assigned to all subsequent days within matched episodes until a new dispensing/prescription is observed or until the end of study follow-up. Tertiles of *current* exposure, based on database-specific values will be created.

9.3.2 Covariates

In each data source, potential differences in CV risk between users of mirabegron and users of antimuscarinic medications will be controlled for by evaluating and adjusting for a broad range of baseline characteristics. The list of pre-specified covariates in the study data sources is summarized in Table 5. These covariates will be included in the PS modeling process as well as additional covariates in the Cox model if imbalances remain, even after matching. Factors include age, sex, geographic area of residence, characteristics that define elevated risk of CV events , relevant diagnoses related to OAB, use of mirabegron and antimuscarinic medications, health care utilization, smoking, obesity, diabetes, alcohol abuse/substance abuse, use of other medications and comorbidities (e.g., COPD, forms of arthritis, renal impairment). In addition to these pre-defined covariates, empirically-identified variables will also be considered. Confounders will be obtained directly or derived from within the baseline data in each data source when available. Otherwise, for variables not well-characterized in the source data, proxies will be used, and estimates from external sources may be used for context.

The covariate-capturing period, which may comprise multiple periods of coverage, will vary in duration for different covariates as some are intended to describe current health status while others aim at describing health history. For example, although only the 12-month period before cohort entry will be used to estimate health care utilization and concomitant medications, other potential covariates will be based on all available information before the cohort entry date (e.g., hypertension). The covariate-capture periods will be outlined in detail in the common Core SAP. Drug use patterns differ between the US and Europe; therefore, the final choice of confounders may vary across data sources. However, common strategies to deal with confounding will be adopted across research sites and are described in the data analysis section. For each data source, a bias analysis[20] will be done to evaluate the potential effect of residual confounding by characteristics that are not well captured in that data source. This assessment will be performed prior to pooling estimates across data sources.

Within each data source, if information on a particular confounding variable is available, patients will be assumed not to have the factor if there is no evidence for its presence (i.e., values for confounder variables used in a given data source will not be considered missing).

The only exception to this principle will be in the situation where "missing" is 1 of the possible values recorded for the variable (e.g., for smoking in the CPRD), in which case the value as listed within the data source will be retained in the analysis as 1 of the possible values (e.g., smoking status in the CPRD can be "smoker," "non-smoker," "former smoker," or "missing").

Table 5 Pre-specified Covariates for Inclusion into the Propensity Score Models (Forced Entry Variables) and Availability by Data Source

Variable(s)	CPRD	ORD and Humana	Danish National Databases	Swedish National Databases
Age (continuous)	Yes	Yes	Yes	Yes
Age (categorical)	Yes	Yes	Yes	Yes
Sex	Yes	Yes	Yes	Yes
Geographic areas (site-specific categories where relevant)	Yes	Yes	Yes	Yes
Separate indicators for use of medications for OAB (mirabegron, any antimuscarinic medications, individual antimuscarinic medications)	Yes	Yes	Yes	Yes
Separate indicators for the number of previous treatment episodes (mirabegron, any antimuscarinic medications, individual antimuscarinic medications)	Yes	Yes	Yes	Yes
Stroke	Yes	Yes	Yes	Yes
Transient ischemic attack (TIA)	Yes	Yes	Yes	Yes
Coronary artery disease	Yes	Yes	Yes	Yes
Angina (diagnosis or medications)	Yes	Yes	Yes	Yes
Acute myocardial infarction (AMI)	Yes	Yes	Yes	Yes
Heart failure	Yes	Yes	Yes	Yes
Arrhythmia (diagnosis or medications)	Yes	Yes	Yes	Yes
Hyperlipidemia (diagnosis or medications)	Yes	Yes	Yes	Yes
Percutaneous Transluminal Coronary Angioplasty (PTCA)	Yes	Yes	Yes	Yes
Coronary Artery Bypass Grafts (CABG)	Yes	Yes	Yes	Yes
Hypertension (diagnosis or medications)	Yes	Yes	Yes	Yes
Antiplatelet medication	Yes	Yes	Yes	Yes
Diabetes (diagnosis or medications)	Yes	Yes	Yes	Yes
Number of hospitalizations (past 12 months)	Yes	Yes	Yes	Yes
Hospitalization (any in past month)	Yes	Yes	Yes	Yes

Table continued on next page

Variable(s)	CPRD	ORD and Humana	Danish National Databases	Swedish National Databases
Number of ER visits (past 12 months)	Yes	Yes	Yes	Not available
Number of outpatient physician office visits (not including labs, diagnostics, or other types of visits, i.e., physical therapy)	Yes	Yes	Yes	Yes
Number of medications (by grouping such as ATC)	Yes	Yes	Yes	Yes
Systemic anti-inflammatory medications (not including nonsteroidal anti-inflammatory drugs)	Yes	Yes	Yes	Yes
Estrogen	Yes	Yes	Yes	Yes
Thyroid replacement medications	Yes	Yes	Yes	Yes
Chronic Obstructive Pulmonary Disease (COPD)	Yes	Yes	Yes	Yes
Dementia	Yes	Yes	Yes	Yes
Gout	Yes	Yes	Yes	Yes
Arthritis	Yes	Yes	Yes	Yes
Renal impairment	Yes	Yes	Yes	Yes
Organ transplantation	Yes	Yes	Yes	Yes
Variables with limited availability				
Obesity (diagnosis codes, procedures, medications)	Yes	Limited	Limited	Limited
Tobacco use (smoking related diagnoses, smoking cessation medications, procedures)	Yes	Limited	Limited	Limited
Alcohol abuse/substance abuse	Yes	Limited	Limited	Limited
Menopause status	poor PPV	Limited	Limited	No

Identification of patients at high risk for CV events.

Patients will be defined as high risk for CV events if, during the 12 months prior to the matched episode, there is evidence of diagnoses, procedures or medications listed below.

Specifically, patients will be considered at high risk if they have:

1) At least 1 of the following diagnoses: stroke, transient ischemic attack , coronary artery disease, angina, AMI, heart failure, arrhythmias (including atrial fibrillation), chronic renal insufficiency, end stage renal disease, peripheral arterial/vascular disease, or
2) At least 1 of the following procedures: percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), carotid endarterectomy, or
3) At least 3 of the following:
    - Hyperlipidemia (diagnosis or relevant medications)
    - Hypertension (diagnosis or relevant medications)
    - Diabetes (diagnosis or relevant medications)
    - Age >= 80 years, or
4) Antiplatelet or anticoagulant medications (excluding aspirin).

9.4 Data Sources

9.4.1 Clinical Practice Research Datalink

CPRD, formerly known as the General Practice Research Database (GPRD), contains the information recorded by GPs as part of their routine clinical practice in the UK (http://www.cprd.com/intro.asp), in addition to linkage to certain other data sources. The CPRD covers approximately 8% of the UK population and includes approximately 5.1 million active users who are alive and currently contribute data to the database. Patients are representative of the whole UK population in terms of age and sex. The database includes approximately 900,000 individuals aged 65 years or older, of which 500,000 are women. Some research has been conducted on OAB treatments in the CPRD.[21]

The following sources of information are available in CPRD:

GOLD: Core data include information on general practice diagnoses, symptoms, referrals, tests ordered, test results, prescriptions issued, and additional clinical information. Prescriptions have fields for strength and dose. Drugs are classified following the British National Formulary, and medical data are coded in the Read coding system. The latter is very granular and is regularly updated in response to user (physician) requests. It has numerous codes for OAB diagnosis, signs, and symptoms.

HES: Admitted Hospital Patient Care, Outpatient, Accident and Emergency (A&E) and Diagnostic Imaging Data (DID). Hospitalization records are coded in ICD-10 codes.

ONS: Death data.

These data are linkable, at least for a large subset of patients, through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency (MHRA). The source population has been divided as follows:

CPRD data linkable (DL) population

A subset of general practices permit linkage to HES data, and the ONS mortality data. The potential cohort members are identified in GOLD. Study outcomes are ascertained from general practice records in the CPRD and via linkage to external data sources - HES data, the ONS mortality data, and data from the other sources if available.

Patients included in the CPRD-DL population will be those whose data can be linked to HES and/or ONS mortality data or other relevant sources of data data.

CPRD not data linkable (NDL) population

A subset of specific general practices does not permit linkage to HES data and the ONS mortality data. The study cohorts and study outcomes are ascertained from general practice records in the CPRD.

9.4.2 Optum Research Database

In the US, the ORD contains medical and pharmacy claims with linked enrollment information with data covering the period from 1993 to the present. One of the largest administrative health care databases in the US, the ORD has 13.9 million health plan members with medical and pharmacy coverage in 2014. Patient identifiers may be accessed in limited instances where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

In addition, medical and pharmacy claims data are available for approximately 3.6 million Medicare enrollees with medical and Part D (prescription) coverage that are enrolled in a managed Medicare program through an offering associated with Optum. Pharmacy claims contain sufficient information to trace patients' pharmacy expenditures through the multiple phases of the Part D plans.

The average length of enrollment in the ORD is approximately 2.4 years and varies considerably within subgroups; thus, eligibility criteria for a particular study can alter the follow-up available considerably. For example, older age groups have longer enrollment, with an average of almost 5 years for those over 50 years of age. The underlying population is geographically diverse across the US. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days supply, financial information, and de-identified patient and prescriber identifiers, allowing longitudinal tracking of medication refill patterns and changes in medications. Medical claims or encounter data are collected from all available health care sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards.[22,23,24]

Patient identifiers may be accessed in limited instances where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

The Medicare Advantage members' claims were not included in the Optum validation study because, at that time, Optum did not have approval for a process that provides access to medical charts for validation purposes within this population.

For both the commercially-insured and Medicare Advantage populations, claims data will be used to identify exposure and covariate information, as well as to identify potential cases but final case status will be determined by data obtained during medical chart adjudication.

9.4.3 Danish National Databases

In Denmark, the Danish health care system provides universal coverage to all Danish residents, approximately 5.6 million individuals in 2013. The centralized Civil Registration System in Denmark allows for personal identification of the entire Danish population through a CPR number, a unique identification number. Use of CPR numbers ensures unambiguous record linkage between all Danish registries, such as the DNPR, which provides data on all admissions to hospitals, the Danish National Prescription Database, and the Danish Registry of Causes of Death. Hospital discharge diagnoses are recorded using ICD-10 codes.

The Danish National Databases are population-based clinical databases on health care data that contain valuable information for epidemiologic research and are linked with each other through the CPR personal identification number.[25] For the purpose of this study the following databases will be used:

The DNPR includes inpatient and outpatient visits to hospitals.[26] It provides data on all admissions to hospitals since January 1, 1977, and on visits to outpatient clinics and emergency departments since 1995. Diagnosis codes are registered by the discharging physician at the time of the hospital discharge. Hospital discharge diagnoses are currently recorded using ICD-10-CM codes.

The Danish Registry of Medicinal Product Statistics provides patient-level data and contains data on all prescription drugs dispensed in community pharmacies since 1995.[27] This database collects data on reimbursed and unreimbursed drugs. Dose and duration of prescription use are not available, but can be derived from the number of prescriptions and the dispensed strength. Drugs are coded using the ATC system.

The Danish Civil Registration System (CRS) was established in1968, where all persons alive and living in Denmark were registered. Among a variety of variables, the CRS contains information on date- and place of birth, gender, residence, emigration / immigration, identity of parents and spouses, and vital status. Information on vital status is daily updated, and follow-up on mortality using the CRS, can be considered fully complete. [28]

The Danish Register of Causes of Death collects data on causes of death.[29] A death certificate must be filed for every Danish decedent. It is filed by the physician with the most accurate knowledge of the events that led to death. Thus, if the decedent was hospitalized at the time

of death, the certificate is filed by a physician working in that hospital department; if the decedent was not hospitalized, it is filed by the decedent's GP. Since 2007, data have been collected electronically.

Earlier versions of this protocol indicated that the DAMD, which contains patients' clinical data and prescription information related to individual consultations with GPs, who provide all primary care data in Denmark, would be included.[30] In 2014, the Danish health authorities have restricted access to this database, so it will no longer be available for this Core study. Loss of this data source has little impact on the quality of the Core studies. The exposure, disease/drug covariates, and the outcomes all have better coverage in the national data resources than in the terminated DAMD database. The only potentially important contribution of the GP database would have been to provide data on lifestyle covariates, such as body mass index (BMI), smoking, and alcohol abuse. Like the other databases, proxies will be used.

9.4.4 Swedish National Databases

In Sweden, all residents are entitled to publicly financed health care covering the entire population, estimated to be 9.6 million in 2013. Many population-based health registries have been established with the use of the unique personal registration number. The personal registration number is given at birth or immigration to all Swedish residents and kept throughout life. In health care, the personal registration number is used for vital statistics and is also the unique identifier and key variable linking different registers. Information in the registers is recorded by current ICD, ICD-O-3, NCSP and/or ATC codes. Data will be obtained from the Total Population Register (with immigrations and emigrations), the NPR (with inpatient and outpatient data), the CDR, and the PDR.

The NPR includes more than 99% of all somatic (including surgery) and psychiatric hospital discharges.[31] It is mandatory for all physicians, private and publicly funded, to deliver data to the NPR (except for visits in primary care). Previous validation of the NPR by the National Board of Health and Welfare showed that 85%-95% of all diagnoses in the NPR are valid.[32] The PDR is a nationwide database covering the entire Swedish population.[33] It includes data that fall into 4 main categories: (1) patient-specific data, (2) prescriber data, (3) drug data, and (4) pharmacy data. Drug data include the trade name, pharmaceutical form, strength and package size, number of packages, ATC classification code, amount in DDD, and the prescribing and dispensing dates. The information is updated monthly. It does not include the majority of sales of non-prescription over-the-counter medicines, medicines administered at hospitals and nursing homes, or medicines prescribed but not dispensed.

9.4.5 Humana Database

The Humana Database contains enrollment information linked to medical, laboratory, and pharmacy claims data for the Humana Medicare Advantage and commercially insured members across the US (~14.2 million total current Humana members as of September 2015). The Humana Database covers the time period from 2007 to present. Cardiovascular outcomes can be validated through medical record review. Diagnoses and procedures in the

Humana claims database were coded according to the ICD-9-CM system until 01 October 2015 when transition to ICD-10 occurred.

Humana is the second largest private Medicare insurer in the US, with over 3 million Medicare Advantage members (with medical and pharmacy benefits) and over 4.5 million Medicare Part D members (with pharmacy benefits only) enrolled as of September 2015. Medicare members over 65 years of age represent the majority of the enrolled population at Humana. The commercially insured account for over 5 million currently enrolled Humana members as of September 2015. CHI has access to Humana's claim-based data set, which combines member enrollment information, medical, pharmacy and laboratory data. The Humana data can be accessed for research purposes for the time period from 2007 to the present. As of September 2015, integrated medical and pharmacy data is available for approximately 10.1 million members.

A unique member identifier is assigned to each individual and remains constant regardless of any gap in plan enrollment or transitions between lines of business (Medicare to commercially insured or vice versa).

Member enrollment data contains coverage start and end dates, date of birth, sex, geographic region, death date, race/ethnicity (for Medicare members only), and insurance line of business, among others. Medical claims data include information related to facility (inpatient) and provider (outpatient) claims, service date, diagnosis code(s), procedure code(s), place of treatment and associated financial data. Diagnoses and procedures in the Humana claims database were coded according to the ICD-9-CM system until 01 October 2015 when transition to ICD-10 occurred. Pharmacy claims data contain outpatient pharmacy claims (excluding over the counter medication information), prescription fill date, National Drug Code (NDC), quantity dispensed, days' supply, and associated financial data. Laboratory data includes service date, diagnosis code(s), Logical Observation Identifiers Names and Codes (LOINC), lab results and lab vendor. Laboratory data are provided via contractual relationships with major national laboratory service providers. Lab results are not available for all members, nor are laboratory data captured comprehensively for those members with available data.

For both the commercially-insured and Medicare Advantage populations, claims data will be used to identify exposure and covariate information, as well as to identify potential cases but final case status will be determined by data obtained during medical chart adjudication.

9.4.6 National Death Index (NDI)

The 2 US data sources (ORD, Humana) will be linked to the NDI to identify patient deaths. The NDI is a central computerized index of cause-of-death information comprising data on file in US state vital statistics offices.[34] The National Center for Health Statistics maintains the database, which contains both date and cause of death for adults and children. The NDI data have approximately a 12-month lag and are updated annually subject to the release schedule determined by the Centers for Disease Control (CDC). As of 31 August 2016 the 2014 NDI Final File is available. Data through the end of 2014 are currently available. To

meet the reporting deadline of June 2019, only claims-identified deaths that occur through December 2016 will be linked using the NDI Plus service, which obtains cause-of-death information.

The completeness of the linkage varies by the amount of information available for each patient (i.e., first name, middle name, last name, date of birth) and is study-specific, but the matching rate in a similar study was over 90%.[35]

The ORD and a corresponding NDI search served as a major data source for an FDA-sponsored CV safety study of medications to treat ADHD in the US.[36] CHI has previously conducted research using administrative claims data supplemented by NDI search, including the validation study conducted as part of the current program (Protocol 178-CL-130).

9.5 Study Size

Study Size

A table summarizing accrual in each of the databases is provided. Patient accrual will continue until the end of each database-specific end of study period.

CPRD, UK

Table 6 shows the number of first-time users as well as prescriptions issued in the CPRD until September 2015. Mirabegron has been used by more than 8,000 patients. It should be noted that the CPRD-linked represents approximately 50% of the CPRD population.

Table 6 Prescriptions for Selected Antimuscarinic and OAB medications, by year (patients aged >=18 and during research quality follow-up in the CPRD primary care data). Clinical Practice Research Datalink, United Kingdom

	2013		2014		2015†	
Drug Name	**Users**	**Prescriptions**	**Users**	**Prescriptions**	**Users**	**Prescriptions**
Darifenacin	334	1,440	371	2,023	355	1,771
Fesoterodine	4,132	24,275	3,979	24,140	2,938	13,383
Oxybutynin	19,679	115,966	17,979	104,798	12,019	54,146
Solifenacin	27,847	174,452	26,990	173,007	20,285	93,508
Tolterodine	11,981	83,497	11,627	77,373	8,795	42,912
Trospium	3,850	24,912	3,390	23,545	2,384	12,478
Mirabegron	1,304	3,735	3,800	17,614	4,189	16,784

† Up through September 2015

ORD, US

During the period of 01 January 2013 to 30 June 2015, there were 129,902 initiators of medications for OAB in the ORD, of which 9,951 initiated mirabegron (see Table 7). These counts are restricted to members who were 18 years or older at the time of first dispensing, had both medical and pharmacy benefits, and had at least 6 months of continuous enrollment prior to the cohort entry date with no claim for the index drug during that 6 month pre-index period.

Table 7 Initiators of Medications for the Treatment of Overactive Bladder, ORD (Commercially Insured and Medicare Advantage Members)

	01JAN2013 – 30JUN2015 Index Year			
	2013	2014	2015†	Total
Drug Name	**N**	**N**	**N**	**N**
Darifenacin	1,533	342	101	1,976
Fesoterodine	4,824	4,061	1,166	10,051
Oxybutynin	29,720	26,550	12,645	68,915
Solifenacin	16,099	7,056	2,688	25,843
Tolterodine	3,214	2,424	1,011	6,649
Trospium	1,531	777	182	2,490
Mirabegron	4,549	3,703	1,699	9,951

†Up through June 2015

Danish National Databases

The number of incident and prevalent users of treatments for OAB during April 2013-June 2015 in Denmark is shown in Table 8.

Table 8 Incident and Prevalent Users of Medications for the Treatment of Overactive Bladder, by Year, Danish National Database

	2013-2015 Index Year			
	2013†	2014	2015††	Total
Drug Name	**N**	**N**	**N**	**N**
Darifenacin	1,050	825	733	2,608
Fesoterodine	5,118	3,956	3,401	12,475
Oxybutynin	306	176	174	656
Solifenacin	17,230	14,927	14,239	46,396
Tolterodine	9,825	9,050	8,661	27,536
Trospium	4,610	3,810	3,764	12,184
Mirabegron	5,796	12,025	15,638	33,459

†Starting April 2013, ††Up through June 2015

Swedish National Databases

The number of incident and prevalent users of medications for the treatment of OAB during 2013-2015 in Sweden is shown in Table 9.

Table 9 Incident and Prevalent Users of Medications for the Treatment of Overactive Bladder from 2013-2015 in Sweden

	2013			2014			2015		
Drug Name	**Men**	**Women**	**All**	**Men**	**Women**	**All**	**Men**	**Women**	**All**
Darifenacin	1,059	1,730	2,789	821	1,232	2,053	423	680	1,103
Fesoterodine	4,994	7,505	12,499	4,066	5,912	9,978	3,400	5,095	8,495
Oxybutynin	1,580	2,467	4,047	1,715	2,630	4,345	1,785	2,779	4,564
Solifenacin	10,469	19,258	29,727	8,957	16,397	25,354	8,312	15,344	23,656
Tolterodine	9,614	14,098	23,712	9,917	13,907	23,824	11,084	15,008	26,092
Mirabegron	2,674	5,442	8,116	7,787	13,658	21,445	10,887	17,530	28,417

Humana Database, US

Between 01 January 2013 and 30 June 2015, there were 3,475 unique members with a first (index) dispensing for mirabegron or antimuscarinic medication, who were 18 years or older at the time of first dispensing, had both medical and pharmacy benefits, and had at least 12 months of continuous enrollment prior to the cohort entry date with no claim for the index drug during that 12 month pre-index period. Counts of potential comparator antimuscarinic medications were also assessed using the same criteria. The results are illustrated in Table 10. Using episode based criteria similar to the specifications in this protocol. There were 8,350 new users of mirabegron in Humana's database including commercially insured and Medicare Advantage enrollees through December 2015.

Table 10 New Users of Medications for the Treatment of Overactive Bladder: 01 Jan 2013 – 30 Jun 2015 Humana Database

	2013	2014	2015†	Total
Drug Name	**N**	**N**	**N**	**N**
Darifenacin	554	285	27	866
Fesoterodine	686	1,099	538	2,323
Oxybutynin	12,234	13,979	8,977	35,190
Solifenacin	5,414	4,861	1,524	11,799
Tolterodine	3,269	3,286	2,097	8,652
Trospium	297	291	141	729
Mirabegron	747	1,735	993	3,475

† Up through June 2015

9.6 Data Management

Files from the various data sources will be kept separate behind firewalls, and the data will not be merged. All data management and analysis will be performed in SAS software (SAS Institute, Inc. Cary, North Carolina) or Stata (StataCorp, College Station, TX).

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

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 selected study staff.

Appropriate data storage and archiving procedures will be followed. Standard procedures to restore files in the event of a hardware or software failure will be in place at each research center.

9.7 Statistical Methods

9.7.1 Sample Size Justification

Sample size estimates are based on matching episodes of new use of mirabegron to episodes of new use of antimuscarinic medications with a 1:1 ratio. A cohort study with 75,000 episodes of patients currently exposed to mirabegron for 2.5 months and the same number of patients exposed to a comparison drug for the same length of time would be able to demonstrate an upper bound of the 95% CI of the IRR lower than 1.5 when the true IRR is 1.00 with a probability of 80%. This estimate is based on the incidence of MACE events in clinical trials for mirabegron (583 per 100,000 person-years), which was observed in patients unexposed to mirabegron but taking a medication indicated for OAB in the clinical development program. It also assumes the average duration of use that was seen in several of the validation studies.

The sample size estimate based on HR rather than IRR is expected to be similar.

In the interim report, updated patient accrual and counts of cases will provide information for an updated estimate of the sample size for the final report.

9.7.2 Data Analysis

Several analyses that are specific to each data source will be conducted for the Interim and Final reports. The details of each analysis will be outlined in the common Core SAP, but a general description of these analyses is provided below.

9.7.2.1 Propensity Score Estimation and Matching

A detailed description of the PS estimation and matching will be provided in the common Core SAP. Briefly, data source-specific PS scores will be estimated using pre-defined and empirically-identified variables, including measures of the number and type of previous exposure episodes. Within each data source, all qualifying episodes of initiation will be identified, separately for mirabegron and each antimuscarinic medication. The probability of starting treatment with mirabegron relative to antimuscarinic medications, conditional on baseline covariates, will be estimated to create a PS. Data source-specific PS matching to balance cohorts with respect to factors present at or before the time of each treatment episode will be conducted. The final decision about inclusion of confounder variables in each population will be based on the availability of the relevant information in each data source and the findings of the validation studies regarding covariate frequency and availability among patients prescribed currently available antimuscarinic medications.

Two cohorts of patients' person-time will be formed by matching episodes of mirabegron use to episodes of antimuscarinic medication use (pooled across all antimuscarinic medications). The cohorts will be PS-matched at a ratio of 1 new episode of mirabegron to 1 new episode of comparator antimuscarinic medication use. A unique PS will be calculated for each new treatment episode that meets the study criteria (i.e., no use of that drug in the prior 12 months, at least 12 months of baseline data available) using the relevant baseline variables for each new episode. For all data sources, a common set of characteristics to include in PSs will be identified and the actual number of codes needed to capture those characteristics will vary by database. The PS estimation model will be built using 3 types of variables: (1) pre-specified variables that exist or can be derived within all databases (e.g., age group, naïve user status), (2) database-unique variables (e.g., length of enrollment in the health plan) and (3) database-unique, empirically defined variables (e.g., most frequent ICD-9 diagnosis codes).

The characteristics of patients who are prescribed a drug that is new to the market often differ from those who are prescribed established medications, and these differences may abate over time. Therefore, to allow the influence of patient characteristics to vary over the study period, episode-based year-specific PS models will be developed and used to create year-specific cohorts. Patients may have more than 1 treatment episode (mirabegron or antimuscarinic medication) within a calendar year, and each episode will be eligible for matching to another episode in the same calendar year, including matching a mirabegron episode to an antimuscarinic medication episode within the same person. Assessments of the extent to which episodes from the same patient match to each other and the number of times they match on more than 1 episode will be evaluated to address the potential need for the models to account for the non-independence of the data.

The PS will be modeled as an unconditional logistic regression model incorporating the predictors of mirabegron episode initiation, with forced entry variables and automated stepwise selection of variables, using the year-specific cohorts (episode-based) of mirabegron users and antimuscarinic medication users. The yearly PS models will be built using all patients who have at least 1 treatment episode in a given calendar year.

To match each mirabegron episode with an appropriate antimuscarinic medication episode, the greedy matching technique described in Parsons, et al will be used.[36] Matches will be restricted to treatment episodes occurring in the same calendar year (corresponding to the year within which the PS is estimated) and two additional matching criteria will be applied: matched patients must be of the same gender and age category (18 to < 65 years old vs 65 years and older). Due to low accrual of mirabegron initiators during the first year of approval in some countries, data from that year may be combined with the subsequent year.

Within each data source, episode-based year-specific PSs will be estimated and pre- and post-matching diagnostics (comparison of patient characteristics) will be performed. Cohort balance will be assessed based on comparison of mirabegron episode characteristics relative to antimuscarinic episode characteristics after matching. If a variable remains unbalanced

after matching, it will be included in the final Cox model. The PS model discrimination after matching will be used as a further diagnostic of balance.

9.7.2.2 Interim Report

The interim report will include data summaries from each of the 5 data sources that will include patient accrual counts and the average (distributions of the) length of observed follow-up in data available up to that point in time (Table 1). Linked data sources (CPRD-linked, Danish Registers, and Swedish Registers) will provide information on the number of AMI and stroke cases and deaths. The data summaries from the US data sources, (ORD and Humana) will include patient accrual counts and length of observed follow-up and also provide the estimated number of AMI and stroke events based on algorithms, the number of charts requested for outcome confirmation, and the number of charts obtained and adjudicated; adjudication status will not be reported (i.e., confirmed case and non-case status). The data summary for the CPRD will include the number of potential outcomes identified and the number of physician surveys to be obtained sought and obtained. For all sites, no comparisons of incidence rates or counts of outcomes by drug (antimuscarinic medications vs mirabegron) will be provided. The report will include a reassessment of power based on projected number of cases and person-time.

9.7.2.3 Final Report

The final report will include results from each of the 5 data sources, as outlined below and summarized in Table 11. Although no individual-level data will be pooled across data sources, meta-analyses of study results (site-specific effect estimates) from each of the data sources will be conducted. The meta-analyses will be the primary study analyses.

Descriptive Analyses

Within each data source (CPRD, ORD, Danish National Databases, Swedish National Databases, Humana Database), baseline characteristics will be determined through review of available data from the time period before initiation, including the initiation day. Comparisons of these baseline characteristics across drug-use cohorts will be presented, before and after PS matching. Descriptive information on the number of dispensings/prescriptions during follow up and the length of follow-up will be summarized. For sites conducting outcome adjudication, summaries of the number of algorithm-identified cases for each outcome and number of adjudicated cases will be provided. The distribution of cumulative dose of mirabegron and antimuscarinic medications will be summarized for each database.

Primary Analyses

Separately within each data source, incidence rates will be calculated as number of events divided by the relevant person-time for each of the different outcomes for the matched episodes of mirabegron use and antimuscarinic medication use. Relative effects as HRs will be derived from Cox proportional hazards models.

All primary analyses will be based on a comparison of mirabegron to antimuscarinic medications (as a group) since the validation studies suggest homogeneity of effect estimates across individual antimuscarinic medications in each data environment. In keeping with the FDA's request, the primary analysis will be an as-treated approach with censoring for switching or end of days supply, in addition to the censoring criteria outlined in Section 9.2.4. The HR comparing events occurring during episodes of current mirabegron use to events occurring during current antimuscarinic medication use among the matched episodes of exposure will be calculated using Cox models. The HR derived from such matched episodes is effectively already adjusted for the components of the PS. However, where certain characteristics appear to remain unbalanced after matching, those variables will be adjusted for in the model. Methods to evaluate the impact of non-independent nature of the data (i.e., multiple episodes per person) on the estimation will be described in the common Core SAP.

Additional primary analyses include restriction to patients aged more than 65 years and restriction to patients at high risk of CV events to address potential residual confounding or effect modification by severity of pre-existing CV conditions. An analysis stratified by prior use of antimuscarinic medications (naïve users vs non-naïve users) will be performed to address drug switching over the course of the study.

Secondary Analyses

A series of secondary analyses will be conducted and are listed in Table 11.

The HR for *current* exposure during various time-since-initiation intervals (< 60 days, 60-<120 days, 120-180 days, >= 180 days) will be evaluated. For patients with multiple qualifying initiations, the outcomes identified during each episode will have a new start for the time-since-initiation since the focus is on *current* exposure.

Although the primary focus of the reports will be on events occurring during *current* exposure, analyses will also include comparisons of the effect of *recent* exposure to mirabegron to *past* mirabegron exposure, comparison of *current* exposure to mirabegron to the incidence within person-time of *past* mirabegron exposure, comparison of *recent* exposure to antimuscarinic medication (as a group) to *past* antimuscarinic medication exposure and comparison of *current* exposure to antimuscarinic medication (as a group) to *past* antimuscarinic medication exposure. Only the first MACE event (e.g., first event of AMI) will be counted during the *current* exposure time for 1 drug, but the same event may be classified as occurring during *recent* or *past* exposure time for another drug. For example, a patient who has an initiation of an antimuscarinic medication and is event-free during the *current* exposure period, may later initiate mirabegron and be observed to have an AMI during *current* mirabegron exposure time. That AMI will be counted in the *current* mirabegron period but will also be counted in the *past* antimuscarinic medication exposure period. The *current*/*recent*/*past* analysis will only be conducted using all antimuscarinic medications as a comparator group so identification of MACE events during switching between antimuscarinic medications does not need to be considered in this analysis. Within a

current exposure episode, however, a patient may be counted as having an AMI for the AMI analysis and as having a stroke within the stroke analysis.

The effect of cumulative dose of mirabegron (in tertiles, *current* exposure only) will be examined, separately within tertiles of mirabegron dose and tertiles of antimuscarinic medications dose, restricted to the most commonly observed medication in each data source. Data source specific tertiles will be used.

One secondary analysis will use a comparator group of individual antimuscarinic medications, in databases with sufficient users. The matched cohorts (mirabegron episodes (current time only) matched to antimuscarinic medication episodes (current time only) will be used – no re-matching by individual medications will be performed.

Generalizability Analysis

Given the difference in patient characteristics and potential confounders across data sources, generalizability of study findings will be assessed. Generalizability for cardiovascular studies usually pertains to differences in effect estimates across strata of underlying cardiovascular risk that might be defined by sex, age, obesity and smoking behavior. Since each data source has an internal comparison group (mirabegron relative to antimuscarinic medications), generalizability of study results is based on the relative CV risk of mirabegron and comparator antimuscarinic medications (as expressed by the HR) across data sources that might differ with respect to the prevalence of different CV risk strata. For each data source, HRs will be reported by sex and by age-specific stratum (18 to <= 44 years, 45 to <=54 years, 55 to <=64 years, 65 to <=74 years, 75 years and older) to evaluate effect modification by age. Since the quality and completeness of obesity and smoking information varies by data source, full examination of HRs by these factors is not likely to be useful. However, each site will provide information on the prevalence of smoking or obesity (or a proxy) and so variations across sites can be assessed.

9.7.2.4 Meta-analysis

The database-specific studies will be conducted according to a common protocol adapted to local database-specific conditions to facilitate future comparison and potential integration of results. No individual-level data will be pooled across data sources, and an appropriate method to combine effect estimates across data sources will be applied, depending on features of the estimates, including the homogeneity of the estimates across populations.

For the interim report, no meta-analysis will be performed. For the final report, all of the primary and secondary analyses outlined in Section 9.7.2 will be performed as meta-analyses.

Recognizing the internal strengths and limitations of each data source, a meta-analytic approach is appropriate, given anticipated heterogeneity in patient characteristics, prescribing patterns, and availability of covariate information. Standard software for combining estimates across data sources, such as RevMan[38] or Comprehensive Meta-Analysis, [39] will be utilized. These software packages perform the meta- analyses and generate diagnostics for assessing heterogeneity along with producing tabular output along with graphical output (forest plot for display of results).

Database-specific estimates (HRs and CIs or exposure-specific events and person-time), will be analyzed using the software package and a summary of the data (tabular and Forest plot) along with pooled estimates and CIs as well as diagnostic measures of heterogeneity will be provided. Results from both random effects and fixed effects meta-analysis will be reported.

Additional details of the planned meta-analyses will be outlined in the common Core SAP.

Table 11 Sequence of Modeling for Cardiovascular Outcomes for Final Report

Analysis	Reporting	
Descriptive Analysis		
Observed number of dispensings/prescriptions and length of follow-up within the mirabegron cohort vs the antimuscarinic medication cohort		Reported by individual data source
Evaluation of baseline characteristics of the treatment cohorts for PS matching		Reported by individual data source
Counts of algorithm-identified vs adjudicated cases for non-linked data sources		Reported by individual data source
Primary Analyses		
HR from Cox models, *current* exposure	Overall	Reported by individual data source and pooled estimates
HR from Cox models, *current* exposure	Restricted to patients age >=65 years old	Reported by individual data source and pooled estimates
HR from Cox models, *current* exposure	Restricted to patients at high risk for CV events	Reported by individual data source and pooled estimates
HR from Cox models, *current* exposure	Stratify by naïve and vs non-naïve new user	Reported by individual data source and pooled estimates
Secondary Analyses		
HR from Cox models: *current* exposure	Stratified by time since initiation: < 60 days, 60 to < 120 days, 120 to < 180 days >= 180 days	Reported by individual data source and pooled estimates
HR from Cox models: *current, recent, past* exposure	$Recent_{mira}$ vs $Past_{mira}$ $Current_{mira}$ vs $Past_{mira}$ $Recent_{anti}$ vs $Past_{anti}$ $Current_{anti}$ vs $Past_{anti}$	Reported by individual data source and pooled estimates
Distribution of cumulative dose for all data sources, *current* exposure only		Reported by individual data source and pooled estimates
HR from Cox models: cumulative dose across tertiles (*current* exposure only) of mirabegron dose	e.g., Compare low mirabegron dose vs high mirabegron dose	Reported by individual data source and pooled estimates

Analysis	Reporting	
Table continued on next page		
HR from Cox models: cumulative dose across tertiles (*current* exposure only) of antimuscarinic medication dose, restricted to the most commonly observed medication in each data source.	e.g., Compare low antimuscarinic medication dose vs high antimuscarinic medication dose	Reported by individual data source and pooled estimates
HR from Cox models: *current* exposure	Individual antimuscarinics as comparator group	Reported by individual data source and pooled estimates

9.8 Quality Control

Within each research center, SOPs will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Key programming modules written by a study analyst might be independently reviewed by a different analyst. The programming will be done by a senior analyst. All key study documents, such as the protocol, abstraction forms, 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).[40]

9.8.1 Non-Interventional Study Monitoring

An independent external SAB has been installed to provide advice on the design, methodological, and analytical considerations for the mirabegron PASS/PMR protocol and corresponding common Core SAP. The SAB is also expected to review relevant and contemporary information such as regulatory authority communications to Astellas surrounding the mirabegron PASS/PMR program and any prior expert advice provided to Astellas, as well as to seek wider input, such as via discussions with epidemiologists, pharmacoepidemiologists, and/or clinicians within the SAB members' network.

9.8.2 Direct Access to Source Documents

Each research partner will maintain copies of the common Core protocol and SAP. In addition, each research partner will prepare a database-specific study protocol and any additional documentation needed to support an FDA audit, if requested.

9.9 Limitations of the Research Methods

The proposed program has several major strengths. One is the large multinational source population that will provide a strong population base to investigate CV risk in association with drugs for OAB in a variety of real-world clinical practice settings. This program will investigate outcomes that have been found to be reliably recorded in automated databases. Furthermore, the presence of the outcomes will be confirmed via medical record review in a

subset of the study population in the CPRD, Humana Database, and the ORD. In addition, this cohort can be the base of future additional outcome or risk minimization effectiveness evaluations, if needed.

The main limitations of this program will be related to the data sources. This program includes analyses from a variety of data sources, each collected for different purposes and over different time periods. In the US, data will be obtained from automated medical and prescription claims and medical records, supplemented with medical chart validation of study outcomes. Although claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the data are collected for the purpose of payment and not research. Drug effects that do not result in billed medical services will not be identifiable. The presence of a claim for a filled prescription or a record of a prescription issued does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over-the-counter or provided as samples by the physician will not be captured. The presence of a diagnosis code on a medical claim is not a conclusive indication of the positive presence of disease, as the diagnosis code may be incorrectly coded or included as a differential diagnosis to be ruled-out, rather than as a diagnosis of actual disease. This is true also of GP-based data sources such as the CPRD. In these data, available clinical information (e.g., results of cardiac enzymes measurements) can be used to increase the PPV of the operational definitions.

Duration of follow-up can be limited in insurance claims databases due to individuals changing health insurance plans. Due to the structure of European health care systems, which are supported through taxation and run by the government, the turnover in the European data sources is low. In the CPRD, follow-up is truncated when patients move and enroll with a practice that does not contribute data to the CPRD, but this is a very small percentage of the population. The CPRD intends to expand its base of contributing practices in the near future (J. Parkinson, director, CPRD, written communication), which would decrease the probability of being transferred out of the network of practices contributing to the CPRD. This problem does not occur in Sweden or Denmark as long as the individual remains in the country. The population in the ORD is representative of the privately insured in the US; however, estimates obtained from these analyses may not be generalizable to the uninsured or to the publicly insured population. The Humana Database contains claims information from Commercial and Medicare insured populations across the US, with higher representation in certain geographic areas where Humana has a larger presence, which may also limit the generalization of the results.

Although methods for confounding adjustment will be implemented through the use of PS matching, residual confounding is always a concern. Confounding will be reduced by extracting information on relevant available study patient characteristics and employing appropriate statistical methodology. During hospitalizations and nursing home stays, completeness of exposure, confounder, and possible outcome data may be affected. Several steps will be taken to minimize these limitations. During the medical chart abstraction process in the validation studies, additional covariate information will be obtained to provide

estimates of the presence of additional unmeasured confounders. Within each database, evaluation to address potential bias from residual confounding will be performed. Examples include smoking, alcohol consumption, and BMI. The methods and potential confounders to be addressed will be outlined in the site-specific protocols. Analysis restricted to patients aged more than 65 years may provide insight into use within an aged population.

9.10 Other Aspects

Not applicable

10 PROTECTION OF HUMAN SUBJECTS

10.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

10.1.1 RTI Health Solutions

RTI International holds a Federal-Wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organization to review and approve human subjects' protocols through the RTI International institutional review board (IRB) committees. RTI-HS will obtain approval from the RTI International IRB for the study.

RTI-HS will seek approval from the CPRD Independent Scientific Advisory Committee (ISAC). This will require that RTI-HS prepare several documents, including a version of the present protocol adapted to ISAC's required format. Proposed questionnaires to be used for validation must be appended to the protocol. Historically, the approval process takes 6-8 weeks and may involve revisions of the submitted documents to address concerns expressed by ISAC members.

10.1.2 Optum

Following health plan approval, an application will be submitted to an IRB and affiliated privacy board (PB) for approval of the medical chart abstraction process and documents. Optum will prepare and submit the appropriate documents to the IRB and affiliated PB. Documents to be submitted for review will likely include the Core study protocol and medical chart abstraction form.

Optum will communicate directly with the IRB and PB to address any questions and/or provide any additional information in connection with the reviews. Astellas will provide any necessary assistance or documents required for the submission to the IRB and PB. Approval from an IRB or PB for this study is not guaranteed. This study will be undertaken only after the study protocol and study documents have been approved and Optum is granted a Waiver of Authorization by the PB. Upon receipt of the Waiver of Authorization from the PB, the IRB will be asked to review and re-approve this study at least once a year. In addition to IRB and PB approval, internal review and approval processes are also required. Upon receipt of the Waiver of Authorization from the PB, Optum will provide a copy of the waiver document

and general study information to the relevant data sources for approval to use such data source's data in the study, which is not guaranteed.

10.1.3 University of Southern Denmark

The conduct of research entails collaboration with a local university or investigator affiliated with a research institute to access the data. Approvals are required from the Danish Data Protection Agency and the National Health Board. According to Danish law, approval from an ethics committee is not required for a database study.[40] All applications have to be submitted in Danish.

10.1.4 Karolinska Institute, Centre for Pharmacoepidemiology

The conduct of research entails collaboration with a local university or investigator affiliated with a research institute to access the data in Sweden. Approval for use of the data from Swedish national health care registers will be requested by CPE from the regional ethical board at KI and from the National Board of Health and Welfare. All applications have to be submitted in Swedish. Only aggregated data will be provided for the meta-analysis, in accordance with Swedish law.

10.1.5 Comprehensive Health Insights

A study synopsis will be submitted to Humana's Protected Health Information and Vendor Ethics (PHIVE) committee for review and approval. The PHIVE committee is chaired by Humana's chief compliance officer and includes representation by legal counsel who specializes in Health Insurance Portability and Accountability Act (HIPAA) regulations, particularly as they pertain to externally funded research. The principal investigator at CHI is responsible for notifying PHIVE of any changes in the study and submitting a bimonthly progress report to PHIVE. Following PHIVE approval and protocol finalization, the principal investigator at CHI will submit the common study protocol and relevant supporting study materials to an independent IRB associated with the submission and a Request for Waiver of Authorization and a Request for Alteration or Waiver of Informed Consent. Only upon receipt of the approval letter and associated waivers will the study be initiated. Regular Continuing Reviews will be submitted on an annual basis to the IRB during the course of the study.

10.2 Ethical Conduct of the Study

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki (2013 or most current version available), ICH E6, and any applicable laws and regulations.

10.3 Patient Information and Consent

Informed consent is not required for medical chart adjudication (ORD, Humana) or for the GP interviews (CPRD), as the data are de-identified.

10.4 Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given to the patient's physician or to other appropriate medical personnel responsible for the patient's well-being, only after approval of the patient. The Sponsor shall not disclose any confidential information on patients obtained during the performance of their duties in this non-interventional study without justifiable reasons.

The Sponsor affirms the patient's right to protection against invasion of privacy. Only a patient identification number and/or initials will identify patient data retrieved by the Sponsor in accordance with national data privacy requirements. However, the Sponsor requires the Investigator(s) to permit the Sponsor, Sponsor's representative(s), the IRB/IEC, and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The approval of the patient should be documented and use of patient identification numbers and/or initials is acceptable, provided that the data are truly anonymized. If this is not possible, patient consent should be obtained, especially if the data in question is sensitive data.

In Sweden, there will be no medical chart review and only registry data will be used for this study. CPE will only have access to anonymized data, i.e., patients cannot be identified to be asked for consent. Individual patient data obtained from the health care registers is considered confidential and disclosure to third parties is prohibited. Data is available from the Swedish National Board of Health and Welfare (registerservice@socialstyrelsen.se) for researchers who meet the criteria for access to confidential data.

10.5 Insurance of Patients

Not applicable

10.6 Other Good Research Practice

The study will be conducted in accordance with the ISPE Guidelines for GPP, [41] the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [42] and guidelines for study conduct and reporting put forth in the FDA's draft guidance document Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.[43]

The ENCePP Checklist for Study Protocols [44] has been completed (see Annex 2), and the study will be registered in the ENCePP study registry. [45]

The study will comply with the definition of the non-interventional (observational) study provided in the EU pharmacovigilance legislation adopted 19 June 2012, [46] and the related Guideline on Good Pharmacovigilance Practices (GVP) module VIII on PASS.[47]

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

According to the new Guideline on GVP, Module VI:

"For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarized in the final study report".[48]

Reporting of adverse events will be performed in accordance with the ISPE Guidelines for GPP.[40]

11.1 Definitions of Adverse Events

Not applicable

11.2 Criteria for Causal Relationship to the (Study) Drug

Not Applicable

11.3 Procedure in Case of Pregnancy

Not Applicable

11.4 Notification of Adverse Drug Reactions (Serious and Non-Serious) by Investigator to Sponsor

Not Applicable

12 PLANS FOR DISSEMINATING AND COMMUNICATION STUDY RESULTS

The combined interim and final study reports will be submitted to the FDA and the EMA.

Study results will be published following the International Committee of Medical Journal Editors guidelines,[1] and communication in appropriate scientific venues, e.g., ISPE conferences, will be considered.

The appropriate STROBE checklist[2] will be followed for study reporting.

13 REFERENCES

1 Validation reports for Studies [178-CL-115], [178-CL-116], [178-CL-118], [178-CL-119], [178-CL-130].
2 International Committee of Medical Journal Editors (ICMJE). Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated December 2015. http://www.icmje.org/urm_main.html. Accessed August 11, 2016.
3 STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement. STROBE checklists (Version 4 as published on Oct/Nov 2007). http://www.strobe-statement.org/index.php?id = available-checklists. Accessed August 11, 2016.
4 Astellas. Research report: mirabegron and cardiovascular disease (New Drug Application 202611). Northbrook, IL: Astellas Pharma Global Development, Inc.; August 2011.
5 Andersson KE, Sarawate C, Kahler KH, Stanley EL, Kulkarni AS. Cardiovascular morbidity, heart rates and use of antimuscarinics in subjects with overactive bladder. BJU Int. 2010 Jul;106(2):268-74.
6 Gopal M, Haynes K, Bellamy SL, Arya LA. Discontinuation rates of anticholinergic medications used for the treatment of lower urinary tract symptoms. Obstet Gynecol. 2008 Dec;112(6):1311-8.
7 Brostrøm S, Hallas J. Persistence of antimuscarinic drug use. Eur J Clin Pharmacol. 2009 Mar;65(3):309-14.
8 D'Souza AO, Smith MJ, Miller LA, Doyle J, Ariely R. Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. J Manag Care Pharm. 2008 Apr;14(3):291-301.
9 Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. Universal definition of myocardial infarction. Circulation. 2007 Nov 27;116(22):2634-53.
10 Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012 Oct 16;126(16):2020-35.
11 Goldman L, editor. Cecil Medicine, 23rd edition. Chapter 430: Approach to cerebrovascular diseases: Saunders; 2007.
12 Kirkman MA, Mahattanakul W, Gregson BA, Mendelow AD. The accuracy of hospital discharge coding for hemorrhagic stroke. Acta Neurol Belg. 2009 Jun;109(2):114-9.
13 Truelsen T, Mähönen M, Tolonen H, Asplund K, Bonita R, Vanuzzo D. Trends in stroke and coronary heart disease in the WHO MONICA Project. Stroke. 2003 Jun;34(6):1346-52.
14 Truelsen T, Mähönen M, Tolonen H, Asplund K, Bonita R, Vanuzzo D. Trends in stroke and coronary heart disease in the WHO MONICA Project. Stroke. 2003 Jun;34(6):1346-52.

15 NHS. Clinical Knowledge Summaries: Stroke and transient ischaemic attack - management. NHS Institute for Innovation and Improvement; 2011. Available at: http://www.cks.nhs.uk/stroke_and_tia. Accessed 26 March 2013.
16 Saver JL. Proposal for a universal definition of cerebral infarction. Stroke. 2008 Nov;39(11):3110-5.
17 García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation. 2004 Jun 22;109(24):3000-6.
18 Cutrona SL, Toh S, Iyer A, Foy S, Daniel GW, Nair VP, Ng D, Butler MG, Boudreau D, Forrow S, Goldberg R, Gore J, McManus D, Racoosin JA, Gurwitz JH. Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program. Pharmacoepidemiol Drug Saf. 2013 Jan;22(1):40-54. doi: 10.1002/pds.3310
19 Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, Goldberg RJ, Gurwitz JH.A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:100-28. doi: 10.1002/pds.2312. Review
20 Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf. 2006May;15(5):291-303
21 Li H, Hodgson E, Watson L, et al. Comorbidities and concomitant medication use in men with prostate cancer or high levels of PSA compared to matched controls: a GPRD analysis. J Cancer Epidemiol. 2012;2012:291704.
22 Dore DD, Liang C, Ziyadeh N, et al. Linkage of routinely collected oncology clinical data with health insurance claims data—An example with aromatase inhibitors, tamoxifen, and all-cause mortality. Pharmacoepidemiology and Drug Safety. 2012;21 Suppl 2:29-36.
23 Ziyadeh N, Fife D, Walker AM, et al. A matched cohort study of the risk of cancer in users of becaplermin. Adv Skin Wound Care. 2011;24(1):31-9.
24 Schneeweiss S, Doherty M, Zhu S, et al. Topical treatments with pimecrolimus, tacrolimus and medium- to high-potency corticosteroids, and risk of lymphoma. Dermatology. 2009;219(1):7-21.
25 Sørensen HT, Christensen T, Schlosser HK, et al. Use of medical databases in clinical epidemiology, 2nd edition.
26 Lynge E, Sandegaard JL, Rebolj M. The Danish National Subject Register. Scand J Public Health. 2011;39(7 Suppl):30-3.
27 Danish Registry of Medicinal Product Statistics. December 11, 2012. Available at: http://www.ssi.dk/English/HealthdataandICT/Health%20data/Registries/Register%20of%20Medicinal%20Products%20Statistics.aspx. Accessed November 20, 2013.
28 Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The danish civil registration system. A cohort of eight million persons. Dan Med Bull. 2006;53:441-449
29 Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health. 2011;39(7 Suppl):26-9.

30 Danish General Practice Quality Unit. Danish General Practice Database. Available at: http://www.dak-e.dk/flx/en/danish-general-practice-database/. Accessed June 13, 2014.
31 Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011 Jun 9;11:450. doi: 10.1186/1471-2458-11-450.
32 Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national in subject register. BMC Public Health. [Validation Studies]. 2011;11:450.
33 Uppsala Universitet. ULSAM. Prescribed Drug Registry data. 2013. Available at: http://www2.pubcare.uu.se/ULSAM/regist/drug/indexdrug.htm. Accessed November 20, 2013.
34 Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin is not associated with a decreased risk of colorectal cancer: a case-control analysis. Cancer Epidemiol Biomarkers Prev. 2012 Feb;21(2):280-6.
35 Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9
36 Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med. 2011 Nov 17;365(20):1896-904.
37 Parsons, L. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. SAS Paper 214-26. http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed August 11, 2016.
38 Cochrane Informatics & Knowledge Management Department. RevMan 5. http://tech.cochrane.org/revman. Accessed August 11, 2016.
39 Comprehensive Meta-Analysis Software (CMA). https://www.meta-analysis.com/. Accessed August 11, 2016.
40 ISPE. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. June 2015 http://www.pharmacoepi.org/resources/guidelines_08027.cfm.Accessed May 23,2016.
41 Danish Data Protection Agency. Introduction to the Danish Data Protection Agency. 2011. Available at: http://www.datatilsynet.dk/english/the-danish-data-protection-agency/introduction-to-the-danish-data-protection-agency/. Accessed February 25, 2014.
42 ENCePP. Guide on methodological standards in pharmacoepidemiology (revision 1). EMA/95098/2010 (amended). European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 11 July 2012. Available at: http://www.encepp.eu/standards_and_guidances/index.shtml. Accessed 8 March 2013.
43 FDA. Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data. US Department of Health and Human Services, Food and Drug Administration; May 2013. Available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf. Accessed 25 February 2014.

44 ENCePP. ENCePP checklist for study protocols (revision 2). European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 14 January 2013. Available at: http://www.encepp.eu/standards_and_guidances/index.shtml. Accessed 8 March 2013.

45 ENCePP. Electronic register of studies. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 2010. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed 8 March 2013.

46 European Commission. Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. 2012. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF. Accessed 8 March 2013.

47 EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-Authorization safety studies. European Medicines Agency; 9 July 2012. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 6 March 2013.

48 EMA. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. European Medicines Agency; 22 June 2012. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed 6 March 2013.

14 ANNEXES

Annex 1.

List of Stand-Alone Documents

Number	Document reference number	Date	Title
1	N/A	10 Nov 2016	List of stand-alone documents
2	N/A	10 Nov 2016	ENCePP checklist
3	N/A	10 Nov 2016	Validation Studies in the CPRD
4	N/A	10 Nov 2016	ICD-10 Codes and Validation Studies
5	N/A	10 Nov 2016	Validity of AMI and Stroke Diagnoses in a Danish Setting
6	N/A	10 Nov 2016	Validation Studies of Registered Diagnoses in Sweden (AMI and stroke)
7	N/A	10 Nov 2016	Substantial Amendment 3

Annex 2.

ENCePP Checklist for Study Protocols

European Network of Centers for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[b]	☒	☐	☐	25
1.1.2 End of data collection[c]	☒	☐	☐	25
1.1.3 Study progress report(s)	☒	☐	☐	25
1.1.4 Interim progress report(s)	☒	☐	☐	25
1.1.5 Registration in the EU PAS register	☐	☒	☐	25
1.1.6 Final report of study results	☒	☐	☐	25

Comments:

In Section 10.6, Other good research practice , it is specified that the study will be registered in the ENCePP study registry

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

[c] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	27
2.1.2 The objectives of the study?	☒	☐	☐	28
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	28
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☒	☐	☐	28
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	--

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	29
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	29
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	50

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	42
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	25
4.2.2 Age and sex?	☒	☐	☐	35
4.2.3 Country of origin?	☒	☐	☐	41
4.2.4 Disease/indication?	☒	☐	☐	35
4.2.5 Co-morbidity?	☒	☐	☐	38
4.2.6 Seasonality?	☐	☒	☐	--
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	35

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Page Number(s)**
5.1	Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	37
5.2	Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	37
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	37
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	37
5.5	Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	38

Comments:

Section 6: Endpoint definition and measurement		**Yes**	**No**	**N/A**	**Page Number(s)**
6.1	Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	29
6.2	Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	29

Comments:

Section 7: Confounders and effect modifiers		**Yes**	**No**	**N/A**	**Page Number(s)**
7.1	Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	38
7.2	Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	38

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	42-47
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	42-47
8.1.3 Covariates?	☒	☐	☐	42-47
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days supply prescription, daily dosage, prescriber)	☒	☐	☐	42-47
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	42-47
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	42-47
8.3 Is a coding system described for:				42-47
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	42-47
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	42-47
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	42-47
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	42-47

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	50

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	50-56
10.2 Is the choice of statistical techniques described?	☒	☐	☐	50-56
10.3 Are descriptive analyses included?	☒	☐	☐	50-56
10.4 Are stratified analyses included?	☒	☐	☐	50-56
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	50-56
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	50-56

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	37,38
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	56
11.3 Are methods of quality assurance described?	☒	☐	☐	56
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	50-56
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	56

Comments:

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

Comments:

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

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Page Number(s)**
14.1	Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	66

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Page Number(s)**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	61
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	61

Comments:

Name of the main author of the protocol: John D. Seeger, PharmD, on behalf of the Research Partners

Date:

Signature: _____

Annex 3.

Validation Studies in the CPRD

Acute Myocardial Infarction

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Varas-Lorenzo C, Garcia-Rodriguez LA, Perez-Gutthann S, et al. Hormone replacement therapy and incidence of acute myocardial infarction. A population-based nested case-control study. Circulation 2000; 101(22): 2572-78	1991-1995	50-74 years old at cohort entry Females	Baseline: Cardio- or cerebrovascular diseases, neoplasms, coagulopathies, vasculitis or alcohol-related diseases Censor if in follow-up: Cardio- or cerebrovascular diseases, neoplasms, coagulopathies, vasculitis or alcohol-related diseases	81.56% (79.31%-83.62%)
García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation 2004;109(24):3000-6	1997-2000	50-84 years old on 1 January 1997 2 years of enrolment with a general practitioner 1 year since first prescription	Baseline: ▪ Cancer ▪ Patients 70 years old and older with scarce contact with general practitioner Censor if in follow-up: ▪ Cancer ▪ 85 years old	95.92% (91.71%-98.33%)
Hammad TA, McAdams MA, Feight A, et al. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2008; 17(12): 1197–201	1997-2004	40-84 years old at cohort entry GPRD quality-related criteria 1 year of baseline information	Baseline: Prior AMI	92.60% (88.30%-95.70%)

AMI = acute myocardial infarction; CI = confidence interval; GPRD = General Practice Research Database.

Stroke

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Arana A, Varas C, González-Pérez A, Gutiérrez L, Bjerrum L, García Rodríguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. Menopause. 2006 Sep-Oct;13(5):730-6	1991-1997	50-59 years old at cohort entry Females	Baseline: ▪ Cardiovascular diseases, neoplasms, coagulopathies, vasculitis, and alcohol-related diseases Censor if in follow-up: ▪ Cardiovascular diseases, neoplasms, coagulopathies, vasculitis, and alcohol-related diseases ▪ 70 years old	Ischemic stroke: 76% Hemorrhagic stroke: 100%
Ruigómez A, Martín-Merino E, Rodríguez LA. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):579-85	2000-2004	40-84 years old in 2000-2004 2 years of enrolment with general practitioner	Baseline: ▪ Cerebrovascular diseases ▪ Cancer Censor if in follow-up: ▪ Cancer ▪ 85 years old	First recorded ischemic stroke: 90.2% (78.6%-96.7%)

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Gaist D, Wallander MA, González-Pérez A, García-Rodríguez LA. Incidence of hemorrhagic stroke in the general population: validation of data from The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2013 Feb;22(2):176-82. doi: 10.1002/pds.3391	2000-2008	40-89 years old Enrolment status: permanent or dead 2 years of enrolment with general practitioner 1 year since the first computerised prescription 1+ visit to primary care practitioner in the previous 2 years	Baseline: ▪ A diagnosis of ICH or subarachnoid hemorrhage before cohort entry ▪ 70+ years old at the start of follow-up with follow-up longer than 1 year and no records in THIN during follow-up Censor if in follow-up: ▪ 90 years old Computer-identified cases were discarded after manual review if: ▪ They were secondary to traumatic injury ▪ They were ischemic instead of hemorrhagic ▪ Not first episode ▪ The patient had cancer or subdural hemorrhage ▪ The episode took place while the patient was hospitalized	Subarachnoid hemorrhage: 91% Intracerebral hemorrhage: 73% Analyses modifying some parts of the outcome definition are also presented; lower confirmation rate in some groups of patients receiving anticoagulant therapy

CI = confidence interval; ICH = intracerebral hemorrhage; THIN = The Health Improvement Network

Annex 4: ICD-10 Codes and Validation Studies

Codes for Acute Myocardial Infarction

ICD-10 Code	Description
I21.x	Acute myocardial infarction
I22.x	Subsequent myocardial infarction

Validation Study for Acute Myocardial Infarction

Reference	Study Period, Location, Type of Data	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value
Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Räihä P, Kärjä-Koskenkari P, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2005 Apr;12(2):132-7	1998-2003 Finnish registries for regions of Finland	Resident of the regions covered by the registries	—	For all definite, probable and possible events: Aged 35-74 years: ▪ Men: 90% ▪ Women: 86% Aged ≥ 75 years ▪ Men: 90% ▪ Women: 86%

Codes for Stroke

ICD-10 Code	Description
H34.1	Acute ischemic stroke, central retinal artery occlusion
I63.x	Acute ischemic stroke, cerebral infarction
I64.x	Stroke, not specified as hemorrhage or infarction
I61.x	Intracerebral hemorrhage
I60.x	Subarachnoid hemorrhage

Validation Studies for Stroke

Reference	Study Period, Location, Type of Data	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Kokotailo RA et al. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. Stroke 2005;36:1776-81	2002-2003 Calgary, Canada Hospital discharge abstracts, including emergency room visits	Stroke code in primary diagnostic position	—	▪ H34.1, I63.x. I64.x: 85% (76%-92%) ▪ I61.x: 98% (92%-99%) ▪ I60.x: 91% (77%-98%)
Kirkman MA, Mahattanakul W, Gregson BA, Mendelow AD. The accuracy of hospital discharge coding for hemorrhagic stroke Acta Neurol Belg. 2009 Jun;109(2):114-9	2002-2007 Newcastle upon Tyne, England Hospital admission records and discharge summaries, including emergency room visits	Hemorrhagic stroke code in primary diagnostic position	—	▪ ICH: 95.9% (94.5%-97.0%) ▪ SAH: 96.1% (94.8%-97.0%)

CI = confidence interval; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage

Validated ICD-10 Codes to Identify Underlying Cause of Death for Potential Community Coronary Heart Disease Deaths

Reference	Code and Description
Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):563-72	I10 Essential hypertension
	I11.9 Hypertensive heart disease, w/o heart failure
	I21 Acute MI (AMI)
	I22 Subsequent MI
	I23 Certain current complications of AMI
	I24 Other acute ischemic heart disease
	I25.2 Old MI
	I20 Angina pectoris
	I25 Chronic ischemic heart disease
	I42.8-.9 Cardiomyopathy, unspecified
	I47.0-.2 Ventricular tachycardia
	I49.0 Ventricular fibrillation and flutter
	I46 Cardiac arrest & sudden cardiac death
	I49.8-.9 Cardiac arrhythmia, unspecified
	I51.9 Heart disease, unspecified
	I51.6 Cardiovascular disease, unspecified
	I70.9 Generalised and unspecified atherosclerosis
	R96.1 Death < 24 hours after symptoms
	R98 Unattended death

AMI = acute myocardial infarction; MI = myocardial infarction

Annex 5: Validity of AMI and Stroke Diagnoses in a Danish Setting

Four studies have validated the accuracy of an AMI diagnosis in a Danish setting, reporting PPVs of 82% to 100%.[1,2,3,4] The estimate of 100% was found in 148 cases coded as AMI, of which all could be verified by manual review. For manifestations of acute coronary syndrome other than AMI, e.g., unstable angina, PPVs may be lower.[5,6]

A further 6 studies have validated the accuracy of a stroke diagnosis in the Danish National Patient Registry.[5,6,7,8,9,10] The PPVs ranged between 79% and 94%.

All of these studies are summarized in the following tables.

[1] Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. J Clin Epidemiol. 2009 Feb;62(2):188-94.

[2] Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol. 2003 Feb;56(2):124-30.

[3] Bjerrum L, Andersen M, Hallas J. Antibiotics active against Chlamydia do not reduce the risk of myocardial infarction. Eur J Clin Pharmacol. 2006 Jan;62(1):43-9.

[4] Coloma PM, Valkhoff VE, Mazzaglia G, Nielsson MS, Pedersen L, Molokhia M, et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ Open. 2013;3(6).

[5] Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A, et al. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Subjects. Clin Epidemiol. 2014;6:27-36.

[6] Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Subjects. Neuroepidemiology. 2007;28(3):150-4.

[7] Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Subjects. J Clin Epidemiol. 2002 Jun;55(6):602-7.

[8] Gaist D, Vaeth M, Tsiropoulos I, Christensen K, Corder E, Olsen J, et al. Risk of subarachnoid hemorrhage in first degree relatives of subjects with subarachnoid hemorrhage: follow up study based on national registries in Denmark. BMJ. 2000 Jan 15;320(7228):141-5.

[9] Bak S, Gaist D, Sindrup SH, Skytthe A, Christensen K. Genetic liability in stroke: a long-term follow-up study of Danish twins. Stroke. 2002 Mar;33(3):769-74.

[10] Østergaard K, Pottegård A, Hallas J, Bak S, Christensen RD, Gaist D. Discontinuation of antiplatelet treatment and risk of recurrent stroke and all-cause death: a cohort study. 2014 submitted.

Validation Studies of Registered Diagnoses in Denmark: Myocardial Infarction

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Coloma PM, Valkhoff VE, Mazzaglia G, et al. EU-ADR Consortium. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ Open. 2013 Jun 20;3(6).	1996-2009	At least 1 year of continuous data about participants in data source before inclusion in cohort	Previous history of heart disease	100%
Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, Tjønneland A, Johnsen S. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. J Clin Epidemiol. 2009 Feb;62(2):188-94.	1993-2003	Aged 50-64 years at cohort entry Resident in urban area of Copenhagen and Aarhus Not registered with a diagnosis of cancer at cohort entry	Diagnosed with ACS before cohort entry	81.9% (79.5%-84.2%)
Bjerrum L, Andersen M, Hallas J. Antibiotics active against Chlamydia do not reduce the risk of myocardial infarction. Eur J Clin Pharmacol. 2006 Jan;62(1):43-9.	1994-1999	Inhabitant of the County of Funen, Denmark, during the study period	—	94%
Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol. 2003 Feb;56(2):124-30.	1982-1991	Aged 25-74 years Resident in 11 municipalities around Glostrup County Hospital in the western suburbs of Copenhagen	Hospitalization for AMI within 28 days prior to event	93.6%

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CI = confidence interval

Validation Studies of Registered Diagnoses in Denmark: Stroke

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A, Johnsen SP. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. Clin Epidemiol. 2013 Dec 23;6:27-36.	2009-2010	Aged ≥ 18 year	Subarachnoid hemorrhage	79%
Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology. 2007;28(3):150-4.	1998-1999	Stroke, TIA, or stroke-related diagnosis in study period Participant in CCHS	Previous diagnosis of stroke Inadequate information obtainable	80.5% (73.6%-86.3%)
Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. J Clin Epidemiol. 2002 Jun;55(6):602-7.	1993-1999	50-64 years old at cohort entry. Resident in urban area of Copenhagen and Aarhus Not registered with a diagnosis of cancer at cohort entry	At any time before enrolment, hospitalized with cardiovascular disease, i.e., stroke, TIA, ischemic heart disease, or peripheral arteriosclerosis	79.3% (74.9%-83.3%)
Gaist D, Vaeth M, Tsiropoulos I, Christensen K, Corder E, Olsen J, Sørensen HT. Risk of subarachnoid hemorrhage in first degree relatives of patients with subarachnoid hemorrhage: follow up study based on national registries in Denmark. BMJ. 2000 Jan 15;320(7228):141-5.	1977-1995	Admission to a hospital in the County of Funen with a diagnosis of SAH within the study period	Admission to a hospital with fewer than 10 registered patients in the study period	SAH: 93% (85%-98%)
Bak S, Gaist D, Sindrup SH, Skytthe A, Christensen K. Genetic liability in stroke: a long-term follow-up study of Danish twins. Stroke. 2002 Mar;33(3):769-74.	1977-1998	Participant in the Danish Twin Registry. Discharged with a stroke diagnosis from hospitals in the County of Funen within the study period	—	85% (79%-90%)

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Østergaard K, Pottegård A, Hallas J, Bak S, Christensen RD, Gaist D. Discontinuation of antiplatelet treatment and risk of recurrent stroke and all-cause death: a cohort study. Submitted 2014.	2007-2011	Participants in the National Indicator Project (NIP). Discharged with a stroke diagnosis from hospital in Region of Southern Denmark	Past stroke diagnoses, use of warfarin	94%

CCHS = Copenhagen City Heart Study; CI = confidence interval; SAH = subarachnoid hemorrhage; TIA = transient ischemic attack

Annex 6: Validation Studies of Registered Diagnoses in Sweden:

Acute Myocardial Infarction

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (n of N)
Hammar N, Alfredsson L, Rosen M, Spetz C-L, Kahan T, Ysberg A-S.A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden, International Journal of Epidemiology 2001; 30:S30-S34.	1987, 1995 AMI	Incident cases of AMI by record linkage of national hospital discharges and deaths 2,065 patients with AMI or other ischemic heart disease 1,848 patients (713 cases and 1,135 non-cases) with medical records	Re*current* event of the same patient within 28 days	PPV 86% (612 of 713) NPV 97% (1,098 of 1,135)
Linnersjo A, Hammar N, Gustavsson A, Reuterwall C. Recent time trends in acute myocardial infarction in Stockholm, Sweden. Int J Cardiol 2000; 76:17-21.	1992–1994 AMI	Study base: aged 30–89 years in 1984–1996 in Stockholm County Evaluated all first AMI cases that occurred in those aged 45–70 years during 1992–1994 2,403 cases identified by combining information of hospital discharges and deaths 2,101 cases with available medical records	Case considered as a first AMI if not registered for a hospital discharge due to AMI for at least the previous 8 years Two discharge registrations for the same person were considered to belong to the same AMI episode if the dates differed less than 28 days	PPV 98% (2,053 of 2,101)
Lindblad U, Råstam L, Ranstam J, Peterson M. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med.1993; 21(1):3-9.	1977-1987 AMI, stroke	Follow-up of a total of 3,240 hypertensive outpatients aged 40-69 years (at index), matched (age, sex, residency, cohort entry year) population controls (census), and normotensive patients from 1977	Only the first non-fatal AMI/stroke events were used, together with all fatal events. Fatal if death occurred within 28 days after the onset, otherwise non-fatal.	PPV 96% (395 of 413) for AMI

AMI = acute myocardial infarction; PPV=positive predictive value; NPV= negative predictive value

Validation Studies of Registered Diagnoses in Sweden: Stroke

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value
Lindblad U, Råstam L, Ranstam J, Peterson M. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med.1993; 21(1):3-9.	1977-1987 AMI, stroke	Follow-up of 3,240 hypertensive outpatients aged 40-69 years (at index), matched (age, sex, residency, cohort entry year) population controls (census), and normotensive patients from 1977	Only the first non-fatal AMI/stroke events were used, together with all fatal events. Fatal if death occurred within 28 days after the onset, otherwise non-fatal.	PPV 94% (236 of 251) for stroke
Stegmayr B, Asplund K. Measuring stroke in the population – quality of routine statistics in comparison with a population-based stroke registry. Neuroepidemiology 1992; 11:204–213.	1985-1989 Non-fatal stroke	Those aged 25 to 74 years discharged from two of nine acute care hospitals, representing 32% of the total target population in the area (northern Sweden) covered by the MONICA registry 5,101 patients discharged alive from hospital WHO MONICA stroke criteria True number extrapolated from case-finding in subsamples to the entire MONICA population	10-20 non-fatal cases with insufficient data (1.6% of all non-fatal cases) 114 non-fatal out-of-hospital stroke events (3.2% of all accepted non-fatal cases in the MONICA registry)	PPV 68.5% (3,492 of 5,101)

AMI = acute myocardial infarction; MONICA = Multinational MONItoring of trends and determinants in CArdiovascular disease; PPV = positive predictive value; WHO = World Health Organization,

Annex 7: Substantial Amendment 3

Substantial Amendment 3 (10 Nov 2016)

I. The purpose of this amendment is:

Substantial Changes
1. Final Report – Full adjudication
DESCRIPTION OF CHANGE: For the final report, rather than rely on algorithms for outcome identification in the ORD, Humana and CPRD-unlinked, adjudication/validation will be completed, when permissions allow.
RATIONALE:
Implemented after recommendations made during the 21 March 2016 FDA Type C meeting in response to: FDA Type C Meeting Minutes issued to Astellas on 04/05/2016, page 6, FDA Response to Question 1b, comment #2.
2. Meta-analysis methods
DESCRIPTION OF CHANGE: Methods for the meta-analysis have been revised and now conform with standard software to pool estimates across published studies.
RATIONALE:
Research Partners discussed methodology and available software for performing meta-analysis and concluded this approach is preferred because it is standardized, generalizable and replicable.
3. Descriptions of the CPRD-linked and CPRD-unlinked data
DESCRIPTION OF CHANGE: Separate descriptions of the CPRD-linked and CPRD-unlinked data have been provided.

RATIONALE:

Implemented after recommendations made during the 21 March 2016 FDA Type C meeting, in response to: FDA Type C Meeting Minutes issued to Astellas on 04/05/2016, page 7, FDA Response to Question 1b, comment #3.

4. Effect measures of interest

DESCRIPTION OF CHANGE:
The statistical methodology has changed from using incidence rate ratios to hazard ratios

RATIONALE:

This change was made to better accommodate the modeling procedures and allow for graphical review of the consistency of the hazard rates over time through the use of Kaplan Meir curves.

5. Revision of sample size estimates

DESCRIPTION OF CHANGE:
The sample size estimates have been revised.

RATIONALE:

This change was made to account for current accrual estimates as well as the use of episodes rather than patients as the unit of analysis.

6. Evaluation of cumulative dose

DESCRIPTION OF CHANGE:
The effect of cumulative dose will be examined only within tertiles of mirabegron and separately within tertiles of antimuscarinic medication (most commonly observed in each data source) rather than by comparing across tertiles of mirabegron vs antimuscarinic medications.

RATIONALE: This change was made by the Research Partners after additional consideration of the most relevant comparisons given the observed differences in individual antimuscarinic medication use across data sources.

15 SIGNATURES

APPROVAL PAGE, RTI Health Solutions

Project Title: Post-authorization Safety Study - Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder

The following people have reviewed the protocol and given their approval:

RTI Health Solutions

Susana Perez-Gutthann, MD, MPH, PhD, FISPE Vice President, Epidemiology	Date

APPROVAL PAGE, Optum

Project Title: Post-authorization Safety Study - Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder

The following people have reviewed the protocol and given their approval:

Optum

John D Seeger, PharmD, DrPH, FISPE Chief Scientific Officer, Epidemiology	Date
Kathleen M. Mortimer, ScD, MPH Director, Epidemiology	Date

APPROVAL PAGE, University of Southern Denmark

Project Title: Post-authorization Safety Study - Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder

The following people have reviewed the protocol and given their approval:

University of Southern Denmark

Jesper Hallas, MD, PhD, FISPE Clinical Pharmacology Professor	Date

APPROVAL PAGE, Centre for Pharmacoepidemiology
Project Title: Post-authorization Safety Study - Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder
The following people have reviewed the protocol and given their approval:

Centre for Pharmacoepidemiology (CPE)

Helle Kieler, MD, PhD; Associate Professor, Head of CPE	Date

APPROVAL PAGE, Comprehensive Health Insights (CHI)
Project Title: Post-authorization Safety Study - Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder
The following people have reviewed the protocol and given their approval:
CHI

Brandon T. Suehs, PharmD, PhD Research Lead	Date
Claudia L. Uribe, MD, MHA, PhD Research Manager	Date

APPROVAL PAGE, Astellas Pharma Global Development, Inc. (APGD)

Project Title: Post-authorization Safety Program - Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder

The following people have reviewed the protocol and given their approval:

Astellas

Milbhor D'Silva, MD, MPH Vice President, Head of Safety Science Pharmacovigilance	Date
Kwame Appenteng, PhD, MPH Epidemiology Director, Epidemiology Pharmacovigilance	Date
Ralph Nies, MD, MBA Vice President, European Qualified Person for Pharmacovigilance	Date