Post-Authorization Safety Program Using the Swedish National Registers—A Validation Study of Cardiovascular and Neoplasm Events in Users of Pharmacological Treatments for Overactive Bladder

Prepared for:
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Swedish Protocol

ISN/Protocol No. 178-CL-118:

A long-term observational study in the Swedish National Registers to prospectively evaluate the incidence of cardiovascular and malignant events (excluding non-melanoma skin cancer) in patients using pharmacological treatments for overactive bladder

Version 1.1, January 8, 2015
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ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitors
AMI	acute myocardial infarction
ARB	angiotensin receptor blockers
BRCA	breast cancer gene
BRCA1	breast cancer 1, early onset gene
BRCA2	breast cancer 2, early onset gene
CDR	Cause of Death Register (Sweden)
CV	cardiovascular
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	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ISPE	International Society for Pharmacoepidemiology
MACE	major adverse cardiac events
NPR	National Patient Register
NPV	negative predictive value
NSAID	nonsteroidal anti-inflammatory drug
OAB	overactive bladder
PASS	postauthorization safety study
PDR	Prescribed Drug Register
PPV	positive predictive value
RR	relative risk
RTI-HS	RTI Health Solutions, a business unit of RTI International
SEER	Surveillance, Epidemiology and End Results Program (US)
SOP	standard operating procedure
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TIA	transient ischemic attack
US	United States

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1 ABSTRACT

Title

Post-Authorization Safety Program Using the Swedish National Registers—A Validation Study of Cardiovascular and Neoplasm Events in Users of Pharmacological Treatments for Overactive Bladder

Version / Date

Version 1.1 / January 8, 2015

Rationale and Background

Mirabegron is a beta-3 adrenergic agonist indicated for the symptomatic treatment of urgency, increased micturition frequency, and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Astellas obtained marketing authorizations for mirabegron on June 28, 2012, in the United States (US)[1] and on December 20, 2012, in the European Union (EU). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) included a post-approval requirement to evaluate cardiovascular safety.[2] The FDA also required a post-approval commitment to evaluate cancer risks.[3]

To prepare for a post-approval safety assessment of cardiovascular (CV) and cancer risk, this study has been designed to describe drug-use patterns among new users of antimuscarinic drugs, calculate background rates of CV and cancer outcomes among antimuscarinic drug users, map the availability of data on covariates, and explore proxies for missing covariates.

Research Question and Objectives

The objectives of this study are as follows:

- To characterize new users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, and tolterodine) with respect to selected covariates.
- To describe the patterns of usage of OAB medications, including duration of treatments, drug switching, and use of medications as add-on therapy to each other.
- To describe the availability of potential confounders in the Swedish national registers.
- To estimate the incidence rates of four different CV events plus all-cause mortality in new users of antimuscarinic drugs indicated for the treatment of OAB.
- To estimate the incidence rate ratio of four different CV outcomes plus all-cause mortality in new users of each of the OAB medications compared with tolterodine, a frequently used OAB medication across the populations of the research program.

- To estimate the incidence rate of two sex-specific, multiple-cancer, composite endpoints (one for men and one for women), during the first year after start of treatment and during subsequent years, among new users of antimuscarinic drugs used in the treatment of OAB.
- To refine the study design, study size, and statistical power assessment for the post-marketing safety studies of mirabegron using the estimated incidences.

Program Design

This will be a retrospective cohort study in the national registers in Sweden. The study period is July 1, 2005, through December 31, 2012, using the first year as run-in to assess new users of OAB treatment.

Population

The cohort will consist of new users of any of the following medications for OAB: oxybutynin, tolterodine, darifenacin, solifenacin, and fesoterodine. A new user is defined at the time of the first dispensing of one of the medications of interest (prescription index date) with at least one year of information and without any previous recorded dispensing of the current study drug that qualifies the subject for cohort entry during the preceding 12 months. Each patient is allowed to contribute exposure time to more than one individual OAB drug.

For each subject, follow-up will start on the date of the first dispensing for a drug of interest and will finish at the earliest of the following events: end of the study period (December 31, 2012), death, emigration, occurrence of an excluded diagnosis, or occurrence of a study endpoint.

Variables

Person-time will be classified based on individual OAB medication dispensing.

The endpoints of interest in the cardiovascular component will be as follows:

1. Acute myocardial infarction (AMI), including coronary heart disease deaths
2. Stroke, including cerebrovascular disease death
3. CV mortality (comprised of coronary heart disease death and cerebrovascular disease death)
4. The composite endpoint major adverse cardiac events (MACE)—CV mortality or death from or hospitalization for acute myocardial infarction or stroke
5. All-cause mortality

Two composite cancer endpoints will be evaluated separately for males and females. The cancers included in the composite endpoints are the 10 cancers with the highest incidence rates in the general population, excluding non-melanoma skin cancer:

1. Males: prostate, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, and pancreas

2. Females: breast, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, corpus uteri, and pancreas

A range of characteristics, including demographics that define elevated cancer risk, relevant diagnoses related to OAB, number of outpatient visits, number of hospitalizations, and use of other medications, will be evaluated.

Data Source

In Sweden, the Prescribed Drug Register (PDR) contains all dispensed prescriptions recorded on an individual level with a personal registration number. The PDR has approximately 6.4 million individuals with at least one dispensing in 2012. The coverage is close to 100% of all prescribed medicines dispensed to the Swedish population. The PDR started July 1, 2005.

For all patients, PDR data are linkable with hospitalization records, the cancer register, and national mortality data. Starting from January 1, 1997, diagnoses in hospital records (in- and outpatients) have been coded according to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10). Procedures are coded according to the Nordic Classification of Surgical Procedures (NCSP), using also the Swedish adaptation “KVÅ.”

Study Size

The study will be conducted in the cohort of new users of any individual OAB medication during the study period.

Data Analysis

The exposure will be defined following initiation of OAB treatment.

The data analysis will include the following activities:

- New users of OAB drugs will be characterized according to baseline covariates.
- Drug use patterns (e.g., discontinuation and switching between antimuscarinic drugs) will be evaluated.
- The ***incidence rate*** of four different CV outcomes plus all-cause mortality during periods of OAB treatment among new users of individual OAB medications will be estimated. Subgroup analyses will target the population aged 65 years or older and individuals with high CV risk.
- The adjusted ***incidence rate ratio*** of four different CV outcomes plus all-cause mortality of each of the OAB medications compared with the most prevalent OAB medication in the PDR (tolterodine) will be estimated.
- The ***incidence rate*** of the two sex-specific ***composite*** neoplasm outcomes will be estimated following initiation of OAB treatment for new users.

- The ***incidence rate*** of the two sex-specific ***composite*** neoplasm outcomes will also be estimated following initiation of OAB treatment among new users of darifenacin, fesoterodine, oxybutynin, solifenacin, and tolterodine while they are not exposed to other OAB medications (that is, exposed to a single OAB).
- A range of potential confounders for CV and neoplasm outcomes are defined, and their distribution and completeness of the information contained in the database will be described.

Milestones

- Final protocol for submission to the FDA: September 8, 2014
- Activities Report submission to the FDA: March 2015
- Final report submission: February 2016

2 ROLES AND RESPONSIBILITIES

Astellas is the study sponsor. The research organizations designing and conducting the mirabegron post-authorization safety program are OptumInsight and Humana in the United States (US), RTI Health Solutions (RTI-HS) in Spain, the Centre for Pharmacoepidemiology (CPE) of the Karolinska Institute (KI) in Sweden, and Syddansk Universitet in Denmark. CPE is responsible for designing the Swedish protocol and conducting the study described in this protocol, using data from the Swedish national registers.

This protocol has been developed by CPE and RTI-HS. Astellas has reviewed the protocol and provided input. Astellas has committed to set up contractual agreements with RTI-HS to coordinate implementation of the study and contract with CPE to conduct the study, granting RTI-HS and CPE independent publication rights in line with the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice,[7] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct,[8] and the International Committee of Medical Journal Editors *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*.[9]

3 PROPOSED STUDY TASKS AND MILESTONES

Task/Milestone	Responsible Party	Timing[a]
Protocol Submission to the FDA	Astellas	Sep 2014
Seek RTI International IRB approval	RTI-HS	July 2014
Submission to Swedish Ethics Committee	CPE	Aug 2014
Swedish ethics approval[b]	CPE	Oct 2014
Development of statistical analysis plan	CPE	Oct 2014

Task/Milestone	Responsible Party	Timing[a]
Apply for data[c]	CPE	Oct 2014
Data delivery[d]	CPE	January 2015
Submission of study status report to the FDA (regulatory milestone)	RTI-HS/Astellas	March 2015
Analytic set completely available	CPE	July 2015
First delivery of tables, documentation, and conclusions to RTI-HS	CPE	Sept 2015
Second delivery of tables, documentation and conclusions to RTI-HS	CPE	November 2015
Draft report of study results	RTI-HS	Dec 2015
Final report of study results	RTI-HS	January 2016
Study report submission to FDA	Astellas	February 2016

CPE=Centre for Pharmacoepidemiology; FDA = Food and Drug Administration; IRB = institutional review board; RTI = RTI International; RTI-HS = RTI Health Solutions.

[a] Contracts between the sponsor and research organization(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalized. The timing of all events depends on completion of previous events; a delay impacts the rest of the timeline.

[b] Requires finalized or almost finalized protocol.

[c] Requires ethical approval, which takes 74 days.

[d] Historically, about 1 to 2 months after application from NBHW; longer for statistics Sweden (up to 6 months).

4 BACKGROUND

4.1 Rationale

Mirabegron is a beta-3 adrenergic 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 once daily. Astellas obtained marketing authorization for mirabegron on June 28, 2012, in the United States (US)[7] and on December 20, 2012, in the European Union (EU).

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.

During the development program, in a 52-week double-blind randomized trial (Study 178-CL-049), there was an imbalance in the number of neoplasms (malignant, benign, or unspecified) among patients randomized to mirabegron 100 mg (11 of 820; 1.3%) compared with those in the mirabegron 50 mg (1 of 812; 0.1%) or tolterodine (4 of 812; 0.5%) groups. In addition, in one of the six OAB 12-week phase 2/3 randomized double-blind studies (Study 178-CL-047),

serious adverse events (SAEs) within the system organ class (SOC) of “Neoplasms benign, malignant, and unspecified (including cysts and polyps)” were observed to be numerically higher in the mirabegron 50 mg (3 of 442; 0.7%) and mirabegron 100 mg (2 of 433; 0.5%) groups than in the placebo group (1 of 453; 0.2%). The numerical imbalance was not observed in the remaining five phase 2/3 studies of the same 12-week duration.

These effects were considered by the regulatory agencies to be potential risks that merited further consideration in a real-world setting. The FDA[8] and European Medicines Agency (EMA) each included a post-marketing (US)/post-approval (EMA) requirement to evaluate cardiovascular safety. The FDA also required a post-marketing commitment to evaluate cancer risks.[9] The post-authorization safety program is designed to address these concerns.

To prepare for a post-marketing safety assessment of cardiovascular (CV) and cancer risk associated with mirabegron use, a study has been designed to describe drug-use patterns among new users of antimuscarinic drugs, to calculate background rates of CV and cancer outcomes in this population. The present protocol describes the study that will be conducted in the Swedish national registers.

4.2 Literature Review

4.2.1 Drug Utilization

A limited number of studies on OAB drug utilization in Sweden have been identified, and key findings are summarized below as they are of relevance for the design of the post-approval safety program.

In an earlier drug utilization study, Altman et al. concluded “from 2000 to 2007, there was a 68.8% increase in dispensed anticholinergic drugs in a population of 9 million. More than 93 million DDDs (calculated average maintenance dose per day) of anticholinergic drugs were dispensed corresponding to an overall DDD/TID (DDD per 1,000 inhabitants per day) of 3.5 per 1,000 persons per year. Approximately two thirds of anticholinergic drugs were prescribed to women, regardless of drug type.”[10]

Linnér et al. reported low adherence to anticholinergic drugs: “Based on the analysis it appears that the adherence rate to continuous treatment with anticholinergics in Sweden is similar to the rate in Denmark.[11] Of the 47,685 individuals who received their first prescription of anticholinergics during 2007 and 2008, less than 50% filled their second prescription within 120 days…After one year the adherence rate was less than 20 percent.”[12]

Johnell and Fastbom identified a potential interaction in the elderly (aged 75 or more years): “Anticholinergic drug use was more common among cholinesterase inhibitor users than non-users, particularly in men, of whom 9% who were taking cholinesterase inhibitors were dispensed anticholinergic drugs compared with 5% who were not taking cholinesterase inhibitors.”[13]

4.2.2 Cardiovascular Risk Factors in Users of Drugs for Overactive Bladder

In a study performed in the HealthCore Integrated Research Database and GE Healthcare database, baseline cardiovascular comorbidity was higher in subjects with an OAB diagnosis or treated with OAB antimuscarinic drugs (39%) than in age- and sex-matched subjects without either OAB codes or OAB antimuscarinic treatment (21%).[14] Cardiovascular comorbidities with a higher prevalence in the OAB group included, among others, hypertension, diabetes, ischemic heart disease, and cardiac conduction disorders. In addition, the prevalence of use of non-OAB drugs with antimuscarinic effect was also higher in the OAB group, 33% vs. 17% for patients without OAB codes or OAB antimuscarinic treatment. Prevalence of cardiovascular comorbidity was similar in OAB patients treated with OAB antimuscarinic drugs (39%) and age- and sex-matched OAB patients with no such treatment (38%); use of non-OAB drugs with antimuscarinic effect was higher in treated subjects (37% vs. 29% for untreated subjects).

A related study, also in the US (GE Healthcare database), found that OAB patients treated with OAB antimuscarinics had baseline heart rate distributions similar to those with no such treatment.[15] In this study, treated OAB patients had a higher proportion of cardiovascular comorbidity (59% vs. 54% for untreated patients), including a higher proportion of hypertension, diabetes, and cerebrovascular disease. However, risk factors for cardiovascular conditions (e.g., age and sex) were not balanced among treated OAB patients (median age, 66 years; 17% men) and untreated OAB patients (median age, 59 years; 14% men).

4.2.3 Outcome Identification and Validation in the Proposed Data Sources

Information on the outcomes for the Swedish component will be extracted from the National Health Registers, which have high diagnostic accuracy.[16] Reporting to the Swedish National Health Registers is mandatory. Appendix A includes a list of validation studies on the outcomes in the data sources.

4.2.3.1 Acute Myocardial Infarction

We found three studies on the validity of AMI diagnoses in the Swedish National Patient Register. Tables with results of these validation studies are included in Appendix A. All of these studies showed the validity of the AMI outcome to be high, with positive predictive values (PPVs) between 86% and 98%.

4.2.3.2 Stroke

We found two studies on the validity of stroke diagnoses in the Swedish National Patient Register. Tables with results of these validation studies are included in Appendix A. All of these studies showed the validity of the stroke outcome to be reasonably high, with PPVs of 68.5% and 94%.

4.2.3.3 Neoplasm

The source of data on cancer outcomes will be the Swedish Cancer Register, which is population based and contains records of all incidences of malignant neoplasms in the Swedish population from 1958 onward. The Swedish Cancer Register is considered to be of good quality, as 99% of the cases are histologically verified, and completeness is high (96.3% in 1998).[17]

5 RESEARCH OBJECTIVES, SPECIFIC AIMS, AND RATIONALE

The objectives of this study are as follows:

- To characterize new users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, or tolterodine) with respect to selected covariates.
- To describe the patterns of usage of OAB medications, including duration of treatments (based on DDDs), drug switching, and use of medications as add-on therapy.
- To describe the availability of potential confounders in the Swedish national registers.
- To estimate the ***incidence rates*** of four different CV events plus all-cause mortality in new users of antimuscarinic drugs indicated for the treatment of OAB.
- To estimate the ***incidence rate ratio*** of four different CV outcomes plus all-cause mortality in new users of each of the OAB medications compared with tolterodine, a frequently used OAB medication across the populations of the research program.
- To estimate the ***incidence rates*** of two sex-specific multiple-cancer, composite endpoints (one for men and one for women), during the first year after start of treatment and during subsequent years, among new users of antimuscarinic drugs used in the treatment of OAB.
- To refine the study size and statistical power assessment for the post-marketing safety studies of mirabegron.

6 DATA SOURCES

The Swedish national health care registers, including the Swedish Prescribed Drug Register, the Swedish Cancer Register, the National Patient Register, and the Causes of Death Register will constitute the primary sources of data.

A unique personal registration number is issued to all residents in Sweden upon birth or immigration and is used throughout life. The unique personal registration number will be used to link patients' data from the different registers described below.[18]

6.1 The Swedish Prescribed Drug Register

Information about patients' drug exposure will be obtained from the Swedish Prescribed Drug Register (SPDR). The SPDR has been functioning since July 2005 and contains data with unique patient identifiers for all prescriptions dispensed to the whole population of Sweden (9.2 million inhabitants).[19] The register is complete for the entire Swedish population (patient identity data are missing for < 0.3% of all items). Data collection is administered by the National Corporation of Swedish Pharmacies, a state-owned company responsible for the provision of pharmaceutical services to the whole country. Information from all prescriptions dispensed is transferred monthly to the National Board of Health and Welfare, which is responsible for keeping the SPDR.[20] The register contains the following data on drugs prescribed and dispensed in ambulatory care: dispensed item (substance, brand name, formulation, and package); dispensed amount, dosage, expenditure, and reimbursement; age, sex, and unique identifier (personal registration number) of the patient; place of residence of the patient (county, municipality, and parish); date of prescribing and dispensing; the practice (primary health care center or hospital clinic) that issued the prescription; and the prescriber's profession (e.g., general practitioner; specialist in internal medicine, psychiatry, or pediatrics).[21] All drugs are classified according to the ATC classification system.[22] Measurement units of utilization are prescriptions, defined daily doses (DDDs), and expenditures. In general, the prescriptions are filled for a maximum of 3 months. The register holds data on dispensed prescriptions and not on prescriptions issued by physicians.

The register does not include data on over-the-counter (OTC) medications or drugs administered in hospitals and does not include complete data on drugs that are used in ambulatory care but are administered during day care at hospitals. The register is not complete with regard to drugs used in nursing homes. Administration of drugs in nursing homes differs between counties. In some counties, all drugs are administered following a prescription whereas in other counties, similar drugs are administered without a prescription. If the study drug is administered to a patient only in the hospital or nursing home, the patient may be misclassified into the unexposed group. However, this situation is expected to be rare as the exposures of interest in this study are usually prescribed in outpatient settings. According to the National Board of Health and Welfare, about 1% of people aged 65-79 years live in nursing homes, and about 20% of people aged 80 or more years live in nursing homes.[23]

6.2 The Swedish Cancer Register

Information on patients' cancer status will be obtained from the Swedish Cancer Register (SCR), which was established in 1958 and covers the whole population of Sweden. All health care providers (public and private, clinicians and pathologists/cytologists) are required by law to report newly detected cancer cases to one of the six regional center registries. A cancer report has to be sent for every cancer diagnosed at clinical, morphological, and other laboratory examinations and those diagnosed at autopsy. The SCR is created annually at the National Board of Health and Welfare by merging data from six regional cancer registers. The relevant medical information available in the SCR comprises site, histological type, and stage of tumor.

The SCR is generally considered to be of good quality as 99% of the cases are histologically verified and the completeness of the SCR is high (96.3% in 1998).[24]

6.3 The National Patient Register

Information on diagnoses will be obtained from the Swedish National Patient Register (NPR), which was started in 1964, initially covering inpatients in six county councils in Sweden. The register covers all public inpatient care since 1987 and all outpatient visits since 2001. The medical data include main and up to 21 secondary diagnoses and up to 30 surgical procedures.[25] Main diagnosis, secondary diagnosis, and procedures from public and private service providers are included in the NPR. A quality control check of the NPR is performed periodically, and in 2006 the main diagnosis was missing from 1.0% of records. At present, the NPR is updated once a year.[26]

6.4 The Cause of Death Register

Information on date and cause of death will be obtained from the Cause of Death Register (CDR), which was established in 1961. Causes of death are classified according to the English version of ICD-10. Since 1987, the Automated Classification of Medical Entities (ACME) system, developed by the National Center for Health Statistics in the United States, has been used to select the underlying cause of death. Automated coding of diagnostic terms reported on the death certificate was introduced in 1993.[27] The main variables included in the mortality register are personal registration number; sex; date of birth; date of death; place of residence; underlying cause of death; main injury; multiple causes of death; autopsy or not and, if so, type of autopsy; death abroad; surgery within 4 weeks before death; intent in cases of injury or poisoning; and place of death by broad categories. The quality of the statistics varies, mainly with the quality and thoroughness of the examination of the cause of death and the accuracy with which the physician has reported the findings on the death certificate. Changes in diagnostic methods, medical concepts and vocabulary, the classification system, or processing methods may also influence time trends.[28]

6.5 Statistics Sweden

The individual socioeconomic characteristics—education, marital status, employment status and information on immigration and emigration—will be obtained from registers held by Statistics Sweden. The total population register holds information on emigration, immigration, and marital status. The register of education holds information about education. Information about employment status comes from the register of labor statistics.

6.6 Study Design Summary

Patients exposed to drugs used in the treatment of OAB will be identified from the population during the study period of July1, 2005, through December 31, 2012. The latter is the latest date for data collection that would allow for completion of the report within the regulatory milestones. This date is consistent across databases in the program.

The characteristics of the patients belonging to the overall exposed cohort and to each category of new users of individual OAB medications will be described, allowing each patient to belong to more than one category. The major risk factors for CV and neoplasm endpoints that could act as potential confounders will be described, and the incidence rates of the four CV endpoints, all-cause mortality, and the two composite neoplasm endpoints in new users of the drugs of interest will be estimated.

6.7 Study Population

Subjects in the program will be required to meet *all* of the following inclusion criteria:

- Be a resident in Sweden for at least 12 months before the first dispensing of an OAB drug of interest (thereby providing medical and prescription history data).
  - For most covariates (e.g., history of bilateral mastectomy, use of hormone-replacement therapy), all available information without time limitation will be used, although the 12-month period prior to the cohort entry date will be used to estimate medical history for conditions identified by ATC codes, number of outpatient visits, and number of hospitalizations.
- Have a first recorded dispensing for oxybutynin, tolterodine, darifenacin, solifenacin, or fesoterodine.
- Be aged 18 years or older at the time of first dispensing of a drug of interest.

Patients will be excluded if they meet *any* of the following criteria at any time prior to cohort entry:

- Had a diagnosis of cancer other than non-melanoma skin cancer between 1997 and cohort entry.
- Had a diagnosis of human immunodeficiency virus (HIV) infection between 1997 and cohort entry.

The latter exclusion criterion has been included in the present protocol for consistency with components of the program that use other data sources. In other data sources, it was expected that the diagnosis of HIV infection would modify the provision of a patient's health care so that it would no longer be captured in the data source. In the Swedish health registers, health care use of subjects with a diagnosis of HIV infection would continue to be captured.

For other comorbidities, including previous CV events and those requiring treatment with potent immunosuppressants, rather than exclude patients, analyses will be stratified to include all patient populations in the study to maximize statistical power and to evaluate the effect modification of these risk factors. This strategy is in keeping with the spirit of the Food and Drug Administration (FDA) *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.[20]

A *new user* of any drug of interest will be a patient who receives a first dispensing for any of the OAB drugs of interest during the study period *without* a dispensing for the same medication in

the previous 12 months. All new users of OAB medications of interest that meet the inclusion criteria will be included in the study.

6.8 Follow-up

Follow-up of eligible subjects will start on the date of the first dispensing of an OAB medication (cohort entry date). For the analyses based on individual endpoints or composite endpoints (either CV or neoplasm), follow-up will finish at the earliest of the following dates:

- End of the study period (December 31, 2012)
- Death
- Emigration
- Occurrence of a diagnosis of human immunodeficiency virus (HIV).
- For all cancer analyses (for both composite and individual cancer endpoints), the first incident targeted cancer is considered to be the cancer endpoint of interest; subsequent or sequential targeted cancer events occurring in the same individual will be ignored, and person-time will be truncated at the occurrence of the first targeted cancer event.
- In the CV analysis, person-time allocation is assigned differently for the composite MACE outcome and for sequential targeted CV events occurring in the same individual.
  - For the composite MACE outcome, person-time follow-up will terminate at the date of occurrence of the first targeted CV event.
  - For sequential targeted CV endpoints occurring in the same individual, person-time of follow-up will continue to accumulate until the date of occurrence of a subsequent targeted CV event. Patients may experience multiple endpoints (e.g., first a stroke and then cancer). Each of these events, and the associated person-time, will be captured.

6.9 Time at Risk and Exposure

6.9.1 Cardiovascular Study

To define time at risk, it is assumed that any cardiovascular effects of OAB medications will present shortly after first use, continue while patients continue the use, and decline after the medication is discontinued.

Each day of exposed person-time will be classified in mutually exclusive categories based on specific drug use and recency of use—current, recent, and past use. Patients will contribute person-time to different exposure categories if they switch treatment. Current use will include the days covered in the prescription plus 7 days, in the understanding that patients may forget doses and use the drug dispensed a few days beyond the days of supply noted in the prescription. Recent use will include the first 60 days after current use, and past use will include person-time after the end of recent use.

The Swedish Prescribed Drug Register does not hold numerical or complete data on the dosing instructions; therefore, the prescription's period of usage may not be inferred directly from the information available. Instead, filled prescriptions will be assigned a period of usage based on the dispensed quantity and the recommended DDD. The evaluation of various exposure metrics will allow for more complete ascertainment of risks associated with different profiles of use.

6.9.2 Neoplasm Study

It is assumed that effects of OAB medications on the incidence of neoplasms will continue for a long period of time after the medication is discontinued. Time at risk will be defined as starting with the first dispensing for new use of any of the OAB drugs.

Follow-up time will extend beyond the end of exposure time, and exposure will be categorized in several ways, as follows:

- Duration of exposure in categories that will correspond to a course of treatment of 1 year, 2 years, and so on.
- Recency of use will also be considered in the exposure classification (i.e., recent use will be defined as any dispensing of the study drug to which a subject is accruing person-time within the previous year, and past use will be defined as beginning 1 year after the most recent prescription was filled).
- Further description of the exposure categories of interest is provided in the data analysis section. Whenever possible, cumulative exposure to study drugs will be defined according to the days of supply of each prescription as the total amount of drug prescribed up to a given point in time, regardless of periods of discontinuation of the drug. Days of supply will be ascertained from the prescription or dispensing information recorded in the data source.

Patients who enter the OAB drug–exposed cohort will be considered "ever exposed" to OAB drugs. For the construction of user categories for single OAB medications, patients who enter the cohort with exposure to OAB drug A will be considered "ever exposed" to OAB drug A.

Patients in the OAB drug A category who subsequently begin treatment with OAB drug B will have their person-time in the OAB drug A category censored at the start of treatment with OAB drug B, and from the date of the first filled prescription of OAB drug B, their person-time will be entered into the category of those exposed to multiple OAB drugs (the multiple-exposure category). Also, from the first the dispensing of OAB drug B the patient will be ever-exposed to B.

6.10 Endpoints

6.10.1 Cardiovascular Endpoints

The endpoints of interest in the cardiovascular component will be as follows:

- Acute myocardial infarction (AMI), including coronary heart disease deaths

- Stroke, including cerebrovascular disease death
- CV mortality (comprised of coronary heart disease death and cerebrovascular disease death)
- The composite endpoint major adverse cardiac events (MACE)—CV mortality or death from or hospitalization for acute myocardial infarction or stroke
- All-cause mortality

The operational definition is described in Section 6.10.3.1 of this protocol.

6.10.2 Neoplasm Endpoints

The neoplasms observed in the mirabegron clinical development program were those that occur commonly in the general population; therefore, the present study will focus on a composite of the 10 most commonly occurring malignancies. Ranking cancers by the highest age-adjusted incidence rate for each sex in the US Surveillance, Epidemiology, and End Results (SEER) data, 2005-2009,[30] these cancers (incidence rate per 100,000, adjusted to the 2000 US standard population) are prostate (69.4), breast (67.2), lung and bronchus (62.6), colon and rectum (46.3), melanoma of skin (21.0), urinary bladder (20.8), non-Hodgkin lymphoma (19.6), kidney and renal pelvis (15.1), corpus uteri (12.6), and pancreas (12.1).

For all cancer analyses (for both composite and individual cancer endpoints), only the first incident targeted cancer is considered to be the cancer endpoint of interest; subsequent or sequential targeted cancer events occurring in the same individual will be ignored, and person-time will be truncated at the occurrence of the first targeted cancer event.

Because several of these cancers occur exclusively (or nearly exclusively) in either males or females, the primary endpoints will be the composite sex-specific incidence rates, as shown in Table 1 (along with the US rates by sex and age):

Table 1. Incidence Rate for Neoplasm Endpoints per 100,000 Person-years in Subjects of All Ages and Those Aged 65 Years or Older, by Sex, United States

	All Ages[a]		Aged ≥ 65 Years[b]	
Type of Cancer	**Males**	**Females**	**Males**	**Females**
Colon and rectum	54	40.2	255.3	191.0
Pancreas	13.8	10.8	76.3	62.0
Lung and bronchus	76.4	52.7	435.8	289.6
Melanoma of the skin	27.2	16.7	125.6	46.4
Breast (female)	—	124.3	—	421.3
Corpus uteri	—	23.5	—	84.8
Prostate	154.8	—	742.2	—
Urinary bladder	37	8.9	222.4	51.1
Kidney and renal pelvis	20.7	10.5	91.2	44.3
Non-Hodgkin lymphoma	23.8	16.3	109.4	75.3
Total per 100,000	**407.7**	**303.9**	**2,058.2**	**1,265.7**

[a] SEER Cancer Statistics Review 1975-2009 Table 1.4. Incidence rates adjusted to 2000 US population. Available at http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php?section=1&page=sect_01_table.04.html. Accessed November 15, 2012.

[b] SEER website Fast Stats – Statistics stratified by age. Data for 2009. Available at: http://seer.cancer.gov/faststats/selections.php?#Output. Accessed November 15, 2012.

Similar data are available for the Swedish population from the NBHW online database, (see Table 2). Most rates are similar to those in the US, but some cancers appear to have a different incidence rate in Sweden; e.g., colon/rectum and melanoma in women and lung/bronchus have a lower rate among the elderly. Some of these differences may depend on the fact that the Swedish data are from 2012 as opposed to the US data (Table 1), which are from 2009.

Table 2. Incidence Rate for Targeted Neoplasm Endpoints per 100,000 Person-years in Subjects of All Ages and Those Aged 65 Years or Older, by Sex, Sweden 2012

	All Ages		Aged ≥ 65 Years	
Type of Cancer	**Males**	**Females**	**Males**	**Females**
Colon and rectum	70.35	63.54	299.07	230.5
Pancreas	10.96	11.15	44.12	40.47
Lung & bronchus	40.26	37.96	176.98	131.74
Melanoma of the skin	36.01	34.76	119.41	77.71
Breast (female)		177.88		436.31
Corpus uteri		28.54		92.38
Prostate	189.3		778.67	
Urinary bladder	39.1	13.18	178.32	49.28
Kidney and renal pelvis	15.21	9.51	57.57	29.34
Non-Hodgkin lymphoma	19.49	15.15	74.07	50.29
Total per 100,000 (sum)[a]	420.68	391.67	1,728.21	1,087.73

Source: National Board of Health and Welfare. Statistics database for cancer. 2012. Available at: http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer. Accessed June 12, 2014.

[a] Patients with more than one of the listed cancers will be counted once for each cancer.

6.10.3 Endpoint Ascertainment and Validation

6.10.3.1 Cardiovascular Endpoints

For CV endpoints, the Swedish National Patient Register contains all cases of AMI and stroke that are diagnosed during hospitalizations. The register collects all information contained in the list of discharge diagnoses for each hospitalization of a Swedish resident with a personal registration number. In addition, fatal cases of AMI and stroke that occur in or out of the hospital are obtained from the National Cause of Death Register, where diagnoses from autopsy reports or death certificates are recorded. As entry of a cause of death is mandatory for every fatality that occurs in the country, the register can be considered to contain all fatal cases of AMI and stroke in Sweden. See Table 3 for high-level ICD-10 codes to be used to identify endpoints in the cardiovascular study. Appendix B contains the ICD-10 codes contained in the definition of each of the endpoints.

Table 3. High-Level ICD-10 Codes for Endpoints in the Cardiovascular Study

Endpoint	ICD-10, National Patient Register	ICD-10, Cause of Death Register
Nonfatal acute myocardial infarction	I21	
Nonfatal stroke	I60-I61, I63–I64	
Coronary heart disease death		I20–I25, I4, I51, I709, R961, R98
Cerebrovascular disease death		I60–I69, G45
All-cause mortality		Any

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

Note: Detailed codes can be found in Appendix B.

The validity of the Swedish Inpatient Register (IPR) is high. The long follow-up makes the register particularly suitable for large-scale population-based research. Ludvigsson et al.[31] reviewed 132 papers that had validated the IPR. With few exceptions, validation of ICD codes from the IPR was made by comparing registered diagnoses in the IPR with information in medical records. The PPV was found to differ between diagnoses in the IPR, but was generally 85%-95%.

We found three studies on the validity of AMI diagnoses in the Swedish National Patient Register and two studies on the validity of stroke. Tables with results of these validation studies are included in Appendix A. All of these studies showed the validity of these outcomes to be high: positive predictive values between 86% and 98% for AMI, and 68.5% and 94% for stroke.

- Linnersjö et al.[32] evaluated the diagnostic quality of the hospital discharge and death records for a total of 2,403 cases of first AMI identified using ICD-9 code 410. Of the 2,101 cases with available medical records (gold standard), 2,053 cases (98%) were classified as AMI according to the diagnostic criteria. A total of 302 fatal cases died outside the hospital. Among the autopsied cases, 93% (193 cases) had died with AMI as an underlying or contributory cause of death. Within the group of 94 unhospitalized fatal cases without autopsy, the corresponding number was 80% (75 cases).
- Hammar et al.[33] collected incident cases of AMI by using ICD-9 code 410 for hospital discharges and deaths. About 40,000 new cases of AMI per year were recorded in Sweden in 1987-1995. Examination of medical records (gold standard) for a national sample of patients with ischemic heart disease (713 cases and 1,135 non-cases) revealed a PPV of 86% and a sensitivity of 94%.
- Lindblad et al.[34] validated AMI and acute stroke by following 3,240 hypertensive patients aged 40-69 years and matched population controls from 1977-1987. The first event suggested in the in-patient register identified by ICD-8 or ICD-9 coding could be confirmed by medical records (gold standard) in 96% (395 of 413) of AMI cases and 94% (236 of 251) of acute stroke cases. The underlying cause of death as identified by ICD-8 or ICD-9 coding in the Cause of Death Register was confirmed by hospital records for 96% (88 of 92) of AMI patients and 92% (36 of 39) of patients with acute stroke.

6.10.3.2 Neoplasm Endpoints

The source of data on cancer outcomes will be the Swedish Cancer Register. The Swedish Cancer Register is population based and contains records of all incidences of malignant neoplasms in the Swedish population from 1958 onward. Reporting to the Swedish Cancer Register is mandatory. The Swedish Cancer Register is generally considered to be of good quality as 99% of the cases are histologically verified, and the completeness of the SCR is high (96.3% in 1998).[35]

6.11 Potential Confounding Factors

In the main analyses of the mirabegron implementation study, we will control for potential differences in distribution of determinants of CV endpoints or in cancer risk between users of antimuscarinic drugs. In the current study, we will describe the study population.

The relevant confounding factors and covariates for CV disease, such as those outlined in Graham et al.,[36] include the following:

- Age
- Sex
- Geographic area of residence
- Characteristics that define high CV risk (e.g., history of cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmias, use of antiarrhythmic drugs, hypertension, use of antihypertensive drugs, hyperlipidemia, use of lipid-lowering drugs, diabetes mellitus)
- Relevant diagnoses related to OAB (e.g., urinary incontinence, urge incontinence)
- Number of outpatient visits and number of hospitalizations
- Use of other medications (e.g., nitrates, other drugs used to treat angina, angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs], antiplatelets, nonsteroidal anti-inflammatory drugs [NSAIDs], estrogen, thyroid hormone replacement)
- Comorbidities (e.g., chronic obstructive pulmonary disease, dementia, gout, forms of arthritis, renal impairment, malignancy, peptic ulcer disease, organ transplantation)

Proxies for characteristics not captured in electronic data, such as smoking, body mass index, alcohol abuse, menopausal status, and occupational exposures or frailty, will be used whenever possible. To address time-varying confounding, the status information for important confounders (such as number of outpatient visits and number of hospitalizations) will be updated during follow-up for the analyses described in the data analysis section. Details will be given in the statistical analysis plan.

In addition to potential CV confounding factors, characteristics that define elevated risk of malignancies, use of other medications (e.g., potent immunomodulators), and comorbidities (e.g., chronic obstructive pulmonary disease, forms of arthritis, renal impairment) will be evaluated.

For most covariates (e.g., history of medical conditions, history of bilateral mastectomy, use of hormone-replacement therapy), all available information from 1997 (start of ICD-10) will be used; however, the 12-month period prior to the cohort entry date will be used to estimate the medical history for conditions identified by ATC codes, the number of outpatient visits, and the number of hospitalizations. Data on drug dispensing are available from July 1, 2005, and ICD-10 coded diagnoses from January 1, 1997.

Table 4 describes the patient characteristic variables available in the Swedish national registers and their format.

Table 4. Description of Patient Characteristic Variables Available in the Swedish National Registers

Patient Characteristic	Type of Variable	Time Window of Assessment	Proxy/Derived/Covered
Birth, cohort entry, cohort exit, death	Date	Specific date	Covered
Cause of death	ICD-10 or other medical codes	Specific date	Covered
Duration of enrolment prior to cohort entry (days)	Number (start date of cohort minus date of enrollment in data source)	Specific period	Derived (enrollment in database at birth or immigration)
Duration of follow-up (days)	Number (date of cohort exit minus the date of cohort entry)	Specific period	Derived
Demographics: age, sex	Age: numerical Sex: binary	Specific fields	Covered
Socioeconomic characteristics: education, marital status, employment status	Categorical: specific categories depend on the data structure	Baseline (just before the cohort entry date)	Covered by Statistics Sweden
Menopause	Binary	Any time before the study period and at event date	Estimated based on age
Hypertension	Binary	Baseline (from July 1, 2005, until cohort entry date)	Derived from ICD-10 and/or ATC
Dyslipidemia	Binary	Baseline (from July 1, 2005, until cohort entry date)	Derived from ICD-10 and/or ATC
History of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, pulmonary artery disease	Binary	Baseline (from July 1, 2005, until cohort entry date)	Derived from ICD-10 and/or ATC and/or NCSP
Diabetes without complications (diabetes with complications is included with the Charlson score)	Binary	Baseline (from July 1, 2005, until cohort entry date)	Derived from ICD-10 and/or ATC
Comorbidities			Derived from ICD-10 and/or ATC and/or NCSP
Alcohol abuse and related conditions	Binary	Baseline (from July 1, 2005, until cohort entry date) and time varying	Weak proxy from ICD-10 and/or ATC and/or NCSP

Patient Characteristic	Type of Variable	Time Window of Assessment	Proxy/Derived/Covered
Drug abuse	Binary	Baseline (from July 1, 2005, until cohort entry date) and time varying	Proxy from ICD-10 and/or ATC and/or NCSP
Comorbidities included in the Charlson Index	Each comorbidity: binary	Baseline (from 1997 until cohort entry date)	Derived from ICD-10
Renal impairment	Binary	Baseline (from 1997 until cohort entry date)	Derived from ICD-10 and/or NCSP
Dialysis	Binary	Baseline (from 1997 until cohort entry date)	Derived from ICD-10 and/or NCSP
Fractures	Binary	Time varying and proxy of frailty	Derived from ICD-10 and/or NCSP
Gout	Binary	Baseline (from July 1, 2005, until cohort entry date)	Derived from ICD-10 and/or ATC and/or NCSP
Arthritis	Binary	Baseline (from July 1, 2005, until cohort entry date)	Derived from ICD-10
Overactive bladder	Binary	Baseline (from July 1, 2005, until cohort entry date)	Derived from ICD-10
Organ transplantation	Binary	Baseline (from 1997 until cohort entry date)	Derived from ICD-10 and/or NCSP
Polycystic ovary syndrome	Binary	Baseline (from 1997 until cohort entry date)	Derived from ICD-10 and/or NCSP
Endometrial polyps or other benign growths of the uterine lining	Binary	Baseline (from 1997 until cohort entry date)	Derived from ICD-10 and/or NCSP

Patient Characteristic	Type of Variable	Time Window of Assessment	Proxy/Derived/Covered
Filled prescriptions Hormone-replacement therapy Tamoxifen use Thyroid hormone replacement Nitrates, digoxin, antidiabetic drugs, statins Non-aspirin NSAIDs Low-dose aspirin[a] Antiplatelets (including aspirin in low doses[a]) Immunosuppressive agents)	Binary	Baseline (from July 1, 2005, until cohort entry date), time varying	Covered
Health services utilization: outpatient visits	Numerical	Baseline (12 months)	Covered
Health services utilization: hospitalizations	Numerical	Baseline (12 months)	Covered
Sigmoidoscopies	Numerical	Baseline (12 months)	NCSP code UJF42 and UJF45

AMI = acute myocardial infarction; BRCA1 = breast cancer 1, early onset gene; BRCA2 = breast cancer 2, early onset gene; CPRD = Clinical Practice Research Datalink; GP = general practitioner; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; NSAID = nonsteroidal anti-inflammatory drug; ONS = Office for National Statistics; PPV = positive predictive value.

[a] Up to 325 mg per tablet.

7 STUDY SIZE

The study is descriptive in nature and will include all new users of the antimuscarinic drugs of interest during the study period.

Table 5 shows the number of prescriptions dispensed in the PDR through December 2012 and the number of patients who received the prescriptions for all ages. Tolterodine and solifenacin are the most frequently prescribed antimuscarinic drugs, in agreement with a prior drug utilization study in the UK in the population of THIN.[37]

Table 5. Prescriptions (Number of Patients) for Selected Antimuscarinic Drugs Through December 2012, Swedish Prescribed Drug Register

Antimuscarinic Drug	2006	2007	2008	2009	2010	2011	2012	Total Dispensed
G04BD07 Tolterodine	256,696 (56,338)	237,145 (50,694)	223,012 (47,058)	196,453 (40,772)	169,894 (34,988)	149,570 (30,616)	126,684 (26,072)	1,359,454
G04BD08 Solifenacin	30,246 (11,885)	43,576 (15,725)	62,121 (20,187)	74,080 (21,969)	88,159 (24,851)	101,393 (28,286)	111,951 (30980)	511,526
G04BD11 Fesoterodine	0 (0)	0 (0)	2,983 (1,965)	19,031 (7,738)	29,234 (10,468)	39,297 (12,800)	45,664 (13,816)	136,209
G04BD04 Oxybutynin	19,314 (6,194)	16,362 (4,830)	14,375 (4,152)	13,458 (4,051)	13,653 (4,319)	13,682 (4,540)	15,059 (4,978)	105,903
G04BD10 Darifenacin	7,644 (3,657)	14,714 (5,907)	14,941 (5,787)	12,029 (4,295)	11,091 (4,191)	11,271 (4,145)	9,807 (3,589)	81,497
G04BD Total	313,900 (73,039)	311,797 (72,361)	317,432 (73,898)	31,5051 (73,445)	312,031 (73,548)	315,213 (75,199)	309,169 (74,865)	2,194,593

8 DATA MANAGEMENT

CPE will apply for the data to the National Board of Health and Welfare and Statistics Sweden. The data sources that will be used in this study will be linked by use of the personal registration number, a unique identifier assigned to all Swedish citizens at birth or upon immigration and kept throughout life. The personal registration number encodes sex and date of birth. All linkage will occur within the NBHW, and anonymized data will be delivered to CPE.

All data management and analysis will be performed in SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina) at the CPE.

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following statistical analysis plans, and performing quality-control checks of all programs.

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, with periodic backup of files to tape. Standard procedures to restore files in the event of a hardware or software failure will be in place.

9 DATA ANALYSIS

9.1 Characterization of Users of OAB Medications

Users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, or tolterodine) will be characterized with respect to a series of selected covariates.

9.2 Drug Dispensing Patterns Description

Patterns of usage of OAB medications, including dose, duration of treatment, drug switching, and use of medications as add-on therapy, will be described.

9.3 Description of the Endpoints and Confounders

In the Swedish component of the program, validation of endpoints against external sources will not be sought because data are considered to be “gold standard.” Data quality processes are in place that ensure adequate quality for research purposes.

Full information on some confounders such as age, sex, comorbidities, and medication use is available. Lifestyle characteristics, such as smoking or alcohol use, are not

available. The study will describe the frequency of the different characteristics of the covariates and will describe the degree of missing information.

9.4 Incidence of Endpoints

Three types of incidence endpoints will be estimated:

- The ***incidence rates*** of four different CV events plus all-cause mortality in new users of antimuscarinic drugs indicated for the treatment of OAB
- The ***incidence rate ratio*** of four different CV outcomes plus all-cause mortality in new users of each of the OAB medications compared with tolterodine, a frequently used OAB medication across the populations of the research program
- The incidence rates of two sex-specific, multiple-cancer composite endpoints (one for men and one for women), during the first year after start of treatment and during subsequent years, among new users of antimuscarinic drugs used in the treatment of OAB

Further details will be provided in the statistical analysis plan.

10 QUALITY ASSURANCE

Internal procedures include rules for secure and confidential data storage, methods to maintain and archive project documents, and requirements for senior scientific review.

All key study documents, such as the statistical analysis plan, abstraction forms, and study reports, will undergo review. Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)*.[38] The EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-Authorisation Safety Studies*, echoes this approach.[36]

At RTI-HS, an independent Office of Quality Assurance (OQA) will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry, data transfer, and institutional review board (IRB) documentation. Such audits will be conducted by the OQA according to established criteria in standard operating procedures and other applicable procedures.

11 STRENGTHS AND LIMITATIONS

The main strength of this study is the use of large, population-based and linked databases: the Swedish national databases cover the entire population of Sweden (9.2 million) and provide a relatively large sample size to study rare events. Misclassification bias of cancer is minimized due to the mandatory reporting and verification procedure of cancer cases. The national register system allows for a

continuous and long follow-up period for the majority of patients. A unique personal registration number, given at birth or immigration and kept throughout life, for each patient allows for linkage of data between databases containing information on the prescription drugs, the outcomes, and the covariates. In addition, this study can produce useful background incidence and validation data for the mirabegron post-approval cardiovascular and neoplasm studies, for which the computer programs generated for the present study can be adapted.

The main weakness of this study is the incomplete capture of potentially important covariates that may be confounding or modifying effects of OAB drugs on CV or cancer outcomes, such as smoking, obesity, and other lifestyle factors. For a number of covariates, proxies will be used to infer the presence of these covariates for members of the cohorts of OAB users. Proxies imperfectly identify the presence of covariates in study subjects, thereby limiting the ability to adjust for these covariates. Also, follow-up may not be long enough for malignancies with a long latency. Another important limitation will be related to the identification of exposure. The record of a prescription dispensed 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. During hospitalizations and nursing home stays, completeness of data on exposure, confounders, and possible outcomes may be affected.

12 PROTECTION OF HUMAN SUBJECTS

12.1 Europe, RTI Health Solutions

12.1.1 Approval by the RTI International IRB

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 a waiver from the RTI International IRB for the study.

12.1.2 Approval by Ethics Committee

CPE will seek approval from the local ethics review board in Stockholm. This will require that CPE prepare several documents, including the final or a close-to-final version of the present protocol.

12.1.3 Approval by the NBHW and Statistics Sweden

CPE will apply for data from the NBHW and Statistics Sweden, both of which will assess the application. This will require that CPE prepare several documents, including the present protocol. To apply for data, an approved ethics application is needed.

13 OTHER GOOD SCIENTIFIC PRACTICE

The study will be conducted in accordance with the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,[40] the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*[41] and guidelines for study conduct and reporting put forth in the FDA guidance document *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.[42] The ENCePP *Checklist for Study Protocols*[43] will be completed, and the study will be registered in the ENCePP study register.[44]

The study will comply with the definition of the noninterventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E*[45] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*,[46] and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012.[47]

14 ADVERSE EVENT REPORTING

For studies in which the research team uses data only from automated health care databases, according to the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,

> *"Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines."*[48]

Thus, reporting of individual cases will not be required, and the analysis of adverse reactions will be based upon aggregated data that are presented in the final study report.

According to the new EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*,

> *"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."*[49]

Module VIII – Post-Authorisation Safety Studies, of the same document echoes this approach.[50] The new legislation further states that for certain study designs such as

retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.

15 COMMUNICATION PLAN

Study protocols and study status and progress reports will be included in regulatory communications in line with regulatory requirements and the following milestones:

- Final protocol submission to the FDA: August 15, 2014
- Activities report submission to FDA: March 31, 2015
- Final report submission to the FDA: February 28, 2016
- Communications to be agreed with the EMA

Astellas has committed to set up contractual agreements with RTI-HS to implement the study, granting RTI-HS independent publication rights in line with the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,[51] ENCePP *Code of Conduct*,[52] and the International Committee of Medical Journal Editors *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*.[53] Study results will be published and communication in appropriate scientific venues, e.g., ISPE conferences, will be considered. The appropriate STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist[54] will be followed for study reporting.

16 PROPOSED RESOURCES TO CONDUCT THE STUDY

16.1 RTI

The project will be led by an epidemiologist at the Director level, who will oversee implementation of the project and writing of the documents and will be in charge of communication with research partners and Astellas, and an epidemiologist at the Vice President level. A senior research epidemiologist will be assigned to the project and will be in charge of the general implementation and drafting of new protocols, the statistical analysis plan, and study results reports. A hematologist/oncologist, an internal medicine specialist, and a cardiologist at the Director level in the epidemiology group will provide clinical expertise.

16.2 CPE

CPE will independently conduct the study, which will be led by a statistician. The statistician will oversee implementation of all aspects of the project at CPE and will be in charge of communication with RTI and with the epidemiologists. Analyses of Swedish

data will be performed at CPE by senior epidemiologists and a senior statistician. The head of CPE will review and approve all deliverables.

17 AMENDMENTS

Table 6. Summary of Amendments and Updates

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
1.1	January 08, 2015	Section 6.8, Follow-up, Section 6.10.2 Neoplasm Endpoints	Refined definition of end of follow-up and of neoplasm endpoints	Clarified that occurrence of only the first study neoplasm is considered to be the cancer endpoint, occurrence of any neoplasm determines end of follow-up, and a subject can experience first a CV endpoint and then a neoplasm endpoint.
1.0	Septem-ber 08, 2014	Original version 1.0	—	—

18 APPENDIX A: VALIDATION STUDIES CONDUCTED IN THE SWEDISH NATIONAL REGISTERS

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Acute Myocardial Infarction

Reference (AMI)	Study Period Endpoint	Inclusion Criteria and Population	Exclusion Criteria	Positive Predictive Value (95% CI)
Hammar N, Alfredsson L, Rosén M, Spetz CL, Kahan T, Ysberg AS. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. Int J Epidemiol. 2001 Oct;30 Suppl 1:S30-4	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 noncases) with medical records	▪ Recurrent event in the same subject within 28 days	PPV, 86% (612 of 713) NPV, 97% (1,098 of 1,135)
Linnersjö A, Hammar N, Gustavsson A, Reuterwall C. Recent time trends in acute myocardial infarction in Stockholm, Sweden. Int J Cardiol. 2000 Oct;76(1):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 during1992–1994 ▪ 2,403 cases identified by combining information from 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 in the previous 8 or more 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 Mar;21(1):3-9.	1977-1987 AMI, stroke	▪ Follow-up of 3,240 hypertensive outpatients aged 40-69 years (index), matched (age, sex, residency, cohort entry year) population controls (census), and normotensive subjects from 1977	▪ Only the first nonfatal AMI/stroke events were used, together with all fatal events ▪ Fatal if death occurred within 28 days after the onset; otherwise nonfatal	PPV, 96% (395 of 413) for AMI

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

Stroke

Reference (Stroke)	Study Period Endpoint	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 Mar;21(1):3-9..	1977-1987 AMI, stroke	▪ Follow-up of 3,240 hypertensive out-patients aged 40-69 years (index), matched (age, sex, residency, cohort entry year) population controls (census), and normotensive subjects from 1977	▪ Only the first nonfatal AMI/stroke events were used, together with all fatal events ▪ Fatal if death occurred within 28 days after the onset; otherwise nonfatal	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(4-6):204-13.	1985-1989 Nonfatal stroke	▪ Patients aged 25-74 years and discharged from two of the nine acute care hospitals, representing 32% of the total target population in the area covered by the MONICA registry (northern Sweden) ▪ 5,101 patients discharged alive from hospital ▪ WHO MONICA stroke criteria ▪ True number extrapolated to the entire MONICA population from case-finding in subsamples	▪ 10-20 nonfatal cases with insufficient data (1.6% of all nonfatal cases) ▪ 114 nonfatal out-of-hospital stroke events (3.2% of all accepted nonfatal cases in the MONICA registry)	PPV, 68.5% (3,492 of 5,101)

PPV = positive predictive value.

19 APPENDIX B: ICD-10 CODES TO BE USED TO IDENTIFY ENDPOINTS IN THE CARDIOVASCULAR STUDY

Cardiovascular Endpoints

Each of the following individual study endpoints will be evaluated in primary analyses:

- Acute myocardial infarction (AMI), including coronary heart disease deaths
- Stroke, including cerebrovascular disease deaths
- CV mortality (comprised of coronary heart disease death and cerebrovascular disease death)
- The composite endpoint major adverse cardiac events (MACE)—CV mortality or death from or hospitalization for acute myocardial infarction or stroke
- All-cause mortality

List of Tables

Table B-1. Acute Myocardial Infarction: ICD-10 Codes (National Patient Register)

ICD-10 Code	Description
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

NOTE: I22 Subsequent myocardial infarction is not included because denotes recurrent, extension or reinfarction occurring within 28 days.

Table B-2. Stroke: ICD-10 Codes (National Patient Register)

ICD-10 Code	Description
I60	Subarachnoid hemorrhage
I60.0	Subarachnoid hemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid hemorrhage from middle cerebral artery
I60.2	Subarachnoid hemorrhage from anterior communicating artery
I60.3	Subarachnoid hemorrhage from posterior communicating artery
I60.4	Subarachnoid hemorrhage from basilar artery
I60.5	Subarachnoid hemorrhage from vertebral artery
I60.6	Subarachnoid hemorrhage from other intracranial arteries
I60.7	Subarachnoid hemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid hemorrhage
I60.9	Subarachnoid hemorrhage, unspecified
I61	Intracerebral hemorrhage
I61.0	Intracerebral hemorrhage in hemisphere, subcortical
I61.1	Intracerebral hemorrhage in hemisphere, cortical
I61.2	Intracerebral hemorrhage in hemisphere, unspecified
I61.3	Intracerebral hemorrhage in brain stem
I61.4	Intracerebral hemorrhage in cerebellum
I61.5	Intracerebral hemorrhage, intraventricular
I61.6	Intracerebral hemorrhage, multiple localized
I61.8	Other intracerebral hemorrhage
I61.9	Intracerebral hemorrhage, unspecified
I63	Cerebral infarction
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I64	Stroke, not specified as hemorrhage or infarction

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

Table B-3. Coronary Heart Disease Death: ICD-10 (Cause of Death Register)

ICD-10 Code	Description
I20	Angina pectoris
I20.0	Unstable angina
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	Subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I23	Certain current complications of acute myocardial infarction
I23.0	Hemopericardium as current complication following acute myocardial infarction
I23.1	Atrial septal defect as current complication following acute myocardial infarction
I23.2	Ventricular septal defect as current complication following acute myocardial infarction
I23.3	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
I23.8	Other current complications following acute myocardial infarction
I24	Other acute ischemic heart disease
I24.0	Coronary thrombosis not resulting in myocardial infarction
I24.1	Dressler’s syndrome

Table B-3. Coronary Heart Disease Death: ICD-10 (Cause of Death Register)

ICD-10 Code	Description
I24.8	Other forms of acute ischemic heart disease
I24.9	Acute ischemic heart disease, unspecified
I25	Chronic ischemic heart disease
I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.2	Old myocardial infarction
I25.3	Aneurysm of heart
I25.4	Coronary artery aneurysm
I25.5	Ischemic cardiomyopathy
I25.6	Silent myocardial ischemia
I25.8	Other forms of chronic ischemic heart disease
I25.9	Chronic ischemic heart disease, unspecified
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, NOS
I46	Cardiac arrest
I46.1	Sudden cardiac death, so described
I46.9	Cardiac arrest, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
I49.8	Other specified arrhythmias
I49.9	Cardiac arrhythmia, unspecified
I51.6	Cardiovascular disease, unspecified
I51.9	Heart disease, unspecified
I70.9	Atherosclerosis, NOS
R96.1	Death < 24 hours after symptoms
R98	Unattended death

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*;
NOS = not otherwise specified;

Table B-4. Cerebrovascular Disease Deaths: ICD-10 (Cause of Death Register)

ICD-10 Code	Description
I60	Subarachnoid hemorrhage
I60.0	Subarachnoid hemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid hemorrhage from middle cerebral artery
I60.2	Subarachnoid hemorrhage from anterior communicating artery
I60.3	Subarachnoid hemorrhage from posterior communicating artery
I60.4	Subarachnoid hemorrhage from basilar artery
I60.5	Subarachnoid hemorrhage from vertebral artery
I60.6	Subarachnoid hemorrhage from other intracranial arteries
I60.7	Subarachnoid hemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid hemorrhage
I60.9	Subarachnoid hemorrhage, unspecified
I61	Intracerebral hemorrhage
I61.0	Intracerebral hemorrhage in hemisphere, subcortical
I61.1	Intracerebral hemorrhage in hemisphere, cortical
I61.2	Intracerebral hemorrhage in hemisphere, unspecified
I61.3	Intracerebral hemorrhage in brain stem
I61.4	Intracerebral hemorrhage in cerebellum
I61.5	Intracerebral hemorrhage, intraventricular
I61.6	Intracerebral hemorrhage, multiple localized
I61.8	Other intracerebral hemorrhage
I61.9	Intracerebral hemorrhage, unspecified
I63	Cerebral infarction
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I64	Stroke, not specified as hemorrhage or infarction

Table B-4. Cerebrovascular Disease Deaths: ICD-10 (Cause of Death Register)

ICD-10 Code	Description
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I65.0	Occlusion and stenosis of vertebral artery
I65.1	Occlusion and stenosis of basilar artery
I65.2	Occlusion and stenosis of carotid artery
I65.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
I65.8	Occlusion and stenosis of unspecified precerebral artery
I65.9	Occlusion and stenosis of unspecified precerebral artery
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I66.0	Occlusion and stenosis of middle cerebral artery
I66.1	Occlusion and stenosis of anterior cerebral artery
I66.2	Occlusion and stenosis of posterior cerebral artery
I66.3	Occlusion and stenosis of cerebellar arteries
I66.4	Occlusion and stenosis of multiple and bilateral cerebral arteries
I66.8	Occlusion and stenosis of other cerebral artery
I66.9	Occlusion and stenosis of unspecified cerebral artery
I67	Other cerebrovascular diseases
I67.0	Dissection of cerebral arteries, nonruptured
I67.1	Cerebral aneurysm, nonruptured
I67.2	Cerebral atherosclerosis
I67.3	Progressive vascular leukoencephalopathy
I67.4	Hypertensive encephalopathy
I67.5	Moyamoya disease
I67.6	Nonpyogenic thrombosis of intracranial venous system
I67.7	Cerebral arteritis, not elsewhere classified
I67.8	Other specified cerebrovascular diseases
I67.9	Cerebrovascular disease, unspecified
I68	Cerebrovascular disorders in diseases classified elsewhere
I68.0	Cerebral amyloid angiopathy
I68.1	Cerebral arteritis in infectious and parasitic diseases classified elsewhere
I68.2	Cerebral arteritis in other diseases classified elsewhere
I68.8	Other cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
I69.0	Sequelae of subarachnoid hemorrhage

Table B-4. Cerebrovascular Disease Deaths: ICD-10 (Cause of Death Register)

ICD-10 Code	Description
I69.1	Sequelae of intracerebral hemorrhage
I69.2	Sequelae of other nontraumatic intracranial hemorrhage
I69.3	Sequelae of cerebral infarction
I69.4	Sequelae of stroke, not specified as hemorrhage or infarction
I69.8	Sequelae of other and unspecified cerebrovascular diseases
G45	Transient cerebral ischemic attacks and related syndromes
G45.0	Vertebrobasilar artery syndrome
G45.1	Carotid artery syndrome (hemispheric)
G45.2	Multiple and bilateral precerebral artery syndromes
G45.3	Amaurosis fugax
G45.4	Transient global amnesia
G45.8	Other transient cerebral ischemic attacks and related syndromes
G45.9 d	Transient cerebral ischemic attack, unspecified

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*;

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