Post-Authorization Safety Program—Validation of the Danish Data Resources for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

Prepared for:

Astellas Pharma Global Development, Inc.

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Danish Study Protocol

ISN/Protocol No.178-CL-119:

A long-term observational study in the Danish Data Resources to prospectively evaluate the incidence and the validity of new cardiovascular and malignant events (excluding non-melanoma skin cancer) in patients using pharmacological treatments for overactive bladder

Version 2.0, February 23, 2015

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ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitors
AMI	acute myocardial infarction
ARB	angiotensin receptor blockers
ATC	Anatomical Therapeutic Chemical classification system
BRCA1	breast cancer 1, early onset gene
BRCA2	breast cancer 2, early onset gene
CV	cardiovascular
DAMD	Danish General Practice Database
DDD	defined daily dose
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-8	*International Classification of Diseases, 8th Revision*
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
ISPE	International Society for Pharmacoepidemiology
MACE	major adverse cardiac events
NORDCAN	A project of the Association of the Nordic Cancer Registries that presents the incidence, mortality, prevalence and survival statistics from 50 major cancers in the Nordic countries.
NSAID	nonsteroidal anti-inflammatory drug
OAB	overactive bladder
PASS	post-authorization safety study
PPV	positive predictive value
RR	relative risk
RTI-HS	RTI Health Solutions, a business unit of RTI International
SDU	University of Southern Denmark/Syddansk University
SEER	Surveillance, Epidemiology and End Results Program (US)
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TIA	transient ischemic attack
US	United States of America

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Version Date: Version 2.0; February 23, 2015

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1 ABSTRACT

Title

Post-Authorization Safety Program—Validation of the Danish Data Resources for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

Version / Date

Version 2.0 / February 23, 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, a validation study has been designed to describe drug-use patterns among users of antimuscarinic drugs, describe the availability of potential confounders, and calculate background rates of CV and cancer outcomes among antimuscarinic drug users. Results of this validation effort will inform the required post-approval safety program to be implemented in the US and the EU.

Research Question and Objectives

The objectives of this study are as follows:

- To characterize users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) 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 describe the availability of potential confounders in the Danish data resources.
- To estimate the incidence rates of CV events in new users of antimuscarinic drugs indicated for the treatment of OAB.
- To estimate the incidence rate ratio of CV outcomes in 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 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.

Program Design

This will be a retrospective cohort study in Denmark. The study period is January 2004 through December 2012.

Population

The cohort will consist of new users of individual OAB medications: oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine. A new user is defined at the time of the first prescription of one of the medications of interest (prescription index date) as having no documented past exposure to the study drug that qualifies the subject for cohort entry. For each subject, follow-up will start on the date of the first prescription for a drug of interest and will finish at the earliest of the following events: end of the study period, death, disenrollment from the database, occurrence of an excluded diagnosis, or occurrence of a study endpoint.

Variables

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

The CV endpoints of interest will be acute myocardial infarction (AMI), stroke, CV mortality (comprised of coronary heart disease death and cerebrovascular disease death), and all-cause mortality. The composite endpoint major adverse cardiac events (MACE)—acute myocardial infarction, stroke, or CV mortality—will also be examined.

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:

- Males: prostate, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, and pancreas
- 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 broad range of characteristics, including demographics, characteristics that define elevated cancer risk, relevant diagnoses related to OAB, health care utilization, and use of other medications will be evaluated.

Data Source

In Denmark, health care data are collected in several nationwide health care databases that can be accessed for research. The current Danish population is approximately 5.6 million persons. Data collected include migration and socioeconomic status, outpatient encounters, hospital discharge records, dispensed prescriptions, and cause of death. Hospitalizations are coded according to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10); drugs are coded in the Anatomical Therapeutic Chemical (ATC) classification system.

Six national data sources will be employed: the Danish National Registry of Patients, the Danish National Prescription Registry, the Central Person Registry, the Taxation Registry, the Cause of Death Registry, and the Danish Cancer Registry. All data will be linked within Statistics Denmark using the Central Person Registry (CPR) number.

Study Size

The study is descriptive in nature and will be conducted in the cohort of new users of individual OAB medications during the study period.

Data Analysis

The cohorts will be defined following initiation of OAB treatment.

The data analysis will include the following activities:

- 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 CV outcomes 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 incidence rate ratio of CV outcomes of each of the OAB medications compared with tolterodine, adjusted for all potential confounders, will be estimated.
- The incidence rate of each composite neoplasm outcome will be estimated following initiation of any OAB treatment among new users of OAB medications, stratified by sex. The incidence rate of each composite neoplasm outcome will also be estimated following initiation of OAB treatment among new users of each OAB medication while they are not exposed to other OAB medications (that is, exposed to a single OAB medication), stratified by sex.
- A wide range of potential confounders for CV and neoplasm outcomes will be defined, and their distribution and completeness of the information contained in the database will be described.

Milestones

- Final protocol submission to the FDA: Q3 2014
- Report submission for the US and EU validation studies: March 2015

2 ROLES AND RESPONSIBILITIES

Astellas is the study sponsor. The four organizations designing and conducting the mirabegron post-authorization safety program are OptumInsight in the United States (US), RTI Health Solutions (RTI-HS) in Spain, the University of Southern Denmark in Denmark, and the Center for Pharmacoepidemiology (CEP) of the Karolinska Institute in Sweden. The University of Southern Denmark is responsible for conducting the study described in this protocol, using Danish data resources. RTI-HS coordinates the overall program in the EU.

This protocol has been jointly developed by the University of Southern Denmark, RTI-HS and Astellas. Astellas will set up contractual agreements with the University of Southern Denmark to implement the study and with RTI-HS to coordinate the overall program in the EU, granting the University of Southern Denmark and RTI-HS independent publication rights in line with the International Society for Pharmacoepidemiology (ISPE) *Good Pharmacoepidemiology Practices*,[4] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) code of conduct,[5] and the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[6]

3 PROPOSED STUDY TASKS AND MILESTONES

Task/Milestone	Responsible Party	Anticipated or Actual Timing
Submission of study protocol to FDA	Astellas	Q3 2014 (end of)
Contracts completed	Astellas/RTI-HS/SDU	Q3 2014 (end of)
EU PAS registration protocol version 2.0	SDU	Q4 2014
Development of statistical analysis plan	SDU	October 2014
Submission to FDA of statistical analysis plan	Astellas	October 2014 (end of)
Start of data collection[a,b]	SDU	Q4 2014
End of data collection[c]	SDU	Q4 2014
Draft 1 report of validation study results	SDU and RTI-HS	February 2015
Final report of validation study results (regulatory milestone)	SDU and RTI-HS	March 2015

FDA = Food and Drug Administration; RTI-HS = RTI Health Solutions; SDU = University of Southern Denmark.

Note: Timelines are based on contract finalization in early September 2014.

[a] Delays in approval from the Danish Data Protection Agency or National Health Board may impact the rest of the timeline. None of the approvals are expected to take longer than 4-6 weeks to process.

[b] Start of data extraction.

[c] Analytic set completely available.

4 BACKGROUND

4.1 Rationale

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, with a recommended starting dosage of 25 or 50 mg daily. Astellas obtained marketing authorization for mirabegron on June 28, 2012, in the United States (US)[1] and on December 20, 2012, in the European Union.

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 potential risks by the regulatory agencies that merited further consideration in a real-world setting. The US Food and Drug Administration (FDA)[2] 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.[3] This 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 users of antimuscarinic drugs, to calculate background rates of CV and cancer outcomes in this population.

The present protocol describes the validation study that will be conducted in the Danish data resources.

4.2 Literature Review

4.2.1 Drug Utilization

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

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.

4.2.2 Cardiovascular Risk Factors in OAB Drug Users

In a study performed in the HealthCore Integrated Research Database and GE Healthcare Database in the US, 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%).[8] 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 patients with OAB treated with OAB antimuscarinic drugs (39%) and age- and sex-matched patients with OAB with no such treatment (38%). The use of non-OAB drugs with antimuscarinic effect was higher in subjects treated with OAB antimuscarinic drugs (37% vs. 29% for untreated subjects with OAB).

A related study, also in the US (GE Healthcare database), found that patients with OAB treated with OAB antimuscarinics had baseline heart rate distributions similar to those with no such treatment.[9] In this study, treated patients with OAB 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 patients with OAB (median age, 66 years; 17% men) and untreated patients with OAB (median age, 59 years; 14% men).

4.2.3 Outcome Identification and Validation in the Data Sources

Several studies have reported predictive values of codes and algorithms used to identify the endpoints of interest in Danish databases.

Acute Myocardial Infarction

A recent validation study on AMI diagnoses was conducted on the Danish Aarhus University Hospital Database, which comprises a prescription registry, a registry of hospital discharge records, a death registry and various others, which can be linked.[10] AMI was defined as the first occurrence of any ICD-10 code for acute myocardial infarction (code I21) in hospital discharge records in years 1996-2009. Of 200 randomly selected cases, medical charts of 148 cases could be accessed and reviewed; the remaining 52 could not be accessed due to the absence of institutional agreements that would have permitted access to the medical charts. All cases were confirmed (positive predictive value [PPV] = 100%).

A validation study sought to validate codes for acute coronary syndrome in the Danish National Registry of Patients.[11] Cases were subjects enrolled in the prospective cohort "Diet, Cancer and Health" aged 50-64 years who had hospital discharge codes for acute coronary syndrome in the primary or secondary positions in years 1993-2003, with no cancer or acute coronary syndrome diagnoses prior to cohort entry. A total of 1,654 potential cases of acute coronary syndrome were identified, of which, medical records for 1,577 were available for review. Of the subset of patients with AMI discharge diagnoses, 1,072 medical charts were reviewed and AMI diagnoses were confirmed in 878 (PPV = 81.9%).

Another study validated cases of hospitalization for AMI in the county of Funen in Denmark.[12] Potential cases were subjects with an AMI discharge record in the Hospital Discharge Registry in years 1994-1999 (ICD-10 codes I21-I22, acute and subsequent myocardial infarction). Hospital discharge letters of a random sample of 500 cases were reviewed for validation of the AMI diagnosis, yielding a PPV of 94%.

Another validation study sought to validate fatal AMIs and AMI hospitalizations from the Danish National Registry of Patients, Registry of Cause of Death, and the National Heart Registry, which combines information from the other two.[13] The reference was the DANMONICA study, a multicenter study that monitored AMI incidence, risk factors, and therapy in 1982-1991. Potential cases were AMIs (identified from ICD-8[*] codes) that occurred in those years in inhabitants of a Copenhagen suburb aged 25-74 years. For AMI as the primary discharge diagnosis or underlying cause of death, the PPV was 93.6%. For AMI as primary or secondary discharge diagnosis, or underlying or contributory cause of death, the PPV was 92.4%.

[*] ICD-8 - *International Classification of Diseases, 8th Revision.*

Stroke

A validation study explored the validity of the diagnosis of stroke in the Danish National Registry of Patients.[14] Potential stroke cases were identified as those with ICD-10 codes I61, I63, and I64 (intracerebral hemorrhage, cerebral infarction, and stroke not specified as hemorrhage or infarction, respectively) in subjects aged 18 years or older hospitalized in 2009. Of 10,015 potential cases, 7,877 were confirmed against medical records, yielding a PPV of 79%.

Another validation study explored the validity of first-ever stroke in subjects enrolled in the prospective Copenhagen City Heart Study.[15] Potential cases were subjects with ICD-10 codes I60, I61, I63, or I64 (subarachnoid haemorrhage, intracerebral hemorrhage, cerebral infarction, and stroke not specified as hemorrhage or infarction, respectively) in the Danish National Register of Patients in years 1998-1999. Hospital discharge letters, medical records, computed tomography, magnetic resonance imaging, angiography, and autopsy reports were reviewed by two reviewers. Of 164 potential stroke cases, one reviewer confirmed 132 (PPV = 80.5%) and the other reviewer confirmed 141 (PPV = 86.0%).

Another validation study investigated the PPV of stroke diagnoses from the Danish National Registry of Patients in patients enrolled in the prospective cohort study “Diet, Cancer and Health.”[16] Potential cases were subjects without prior hospitalizations for cardiovascular or cerebrovascular conditions aged 50-64 years with ICD-10 codes I60, I61, I63, or I64 (see description of codes provided previously) in the primary or secondary positions in the National Patient Registry in years 1993-1998 (Copenhagen) or 1993-1999 (Aarhus). Case confirmation was based on review of medical records (including reports from imaging studies and laboratory test results) and hospital discharge letters. The PPV was 79.3% for the 377 potential cases identified.

In a study looking at subarachnoid hemorrhage in relatives of persons who had a subarachnoid hemorrhage in Funen County in years 1977-1995,[17] potential cases identified in the National Patient Registry (ICD-10 codes I60 and analogous ICD-8 codes) were confirmed through review of medical records, discharge abstracts, and autopsy reports. Subjects with concurrent codes for arteriovenous malformations were excluded. The authors reported misclassification of less than 20% in the 191 incident events identified, with differences depending on the type of ward from which the patient was discharged (neurosurgery, neurology, or others).

A study that explored the risk of stroke in twins validated stroke diagnoses in the National Discharge Registry against discharge abstracts.[18] Potential cases were twins registered in the Danish Twin Registry and living in Funen County who had codes for stroke in the National Discharge Registry (I61, I63 and I64 ICD-10 codes, and analogous ICD-8 codes) in years 1977-1998. Of 333 potential events identified, records for 288 were accessible, with a PPV of 85%.

Neoplasm Endpoints

One study validated the diagnosis of female breast cancer in the Danish Cancer Registry in residents of Aarhus County.[19] Potential cases were subjects with breast cancer records in the Danish Cancer Registry, the Danish Breast Cancer Cooperative Group (which collects information related to breast cancer in clinical trials), and the local oncology department registry (which provided administrative information) in years 1983-1989. Exclusion criteria for validation were information from the death certificate as the sole source; no clinical information; no histopathological diagnosis; previous history of invasive cancer; benign tumors or carcinoma in situ; surgery outside the county; unknown primary tumor; and tumors other than carcinoma. From the 1,749 potential cases, the percentage of clinical information correctly identified in the registry was 99%.

Another study ascertained the validity of brain tumors in a pediatric population in the Danish Cancer Registry for the period 1980-1996.[20] By manual review of medical records for 640 cases reported to the Danish Cancer Registry, 98% of the brain tumors could be verified. The recorded histopathological classification in the Danish Cancer Registry was correct in 82% of cases for which a histopathological diagnosis was available. This proportion varied by histopathological diagnosis and was 84% for astrocytomas, 88% for ependymomas, and 95% for medulloblastomas. Other, more rare tumors had a lower level of accuracy.

A study from 1985 ascertained the coverage (sensitivity) of the Danish Cancer Registry, by cross-referencing all records from 1977 with all cancer diagnoses found in the Danish National Registry of Patients.[21] No case validation was carried out. Of 23,228 cancer cases that were found in either registry, 21,740 (94%) could be found in the Danish Cancer Registry. It should be noted that since 2004, all cancers in the Danish National Registry of Patients are routinely reported to the Danish Cancer Registry (see Section 6.6.3.2 on ascertainment of Neoplasm Endpoints).

5 RESEARCH OBJECTIVES, SPECIFIC AIMS, AND RATIONALE

The objectives of this study are as follows:

- To characterize users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium) 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 describe the availability of potential confounders in the Danish data resources.
- To estimate the incidence rates of CV events in new users of antimuscarinic drugs indicated for the treatment of OAB.

- To estimate the incidence rate ratio of CV outcomes in 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 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

Six different national data sources will be employed:

- The Danish National Registry of Patients*
- The Danish National Prescription Registry*
- The Central Person Registry*
- The Taxation Registry*
- The Cause of Death Registry
- The Danish Cancer Registry

All data sources will be linked using the Central Person Registry number, a unique identifier assigned to all Danish residents since 1968 that encodes sex and date of birth. All linkage will occur within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes. Confidentiality is ensured by several layers of password-protected sign-in, use of a real-time password assigned by a remote token, use of de-identified data, and the fact that researchers cannot extract data from Statistics Denmark, only the output of their analyses[22]

6.1.1 The Danish National Registry of Patients

The Danish National Registry of Patients contains data on all secondary care contacts in Denmark since 1977. From 1995 onward, outpatient diagnoses have been included systematically. Discharge diagnoses were coded according to ICD-8 from 1977 through 1993 and ICD-10 since 1994. Virtually all medical care in Denmark is furnished by the public health authorities, whereby this data resource allows true population-based studies covering all inhabitants of Denmark.[23]

* Hosted in Statistics Denmark. Data from the other data sources will be transferred to Statistics Denmark for the purpose of this study.

6.1.2 Danish National Prescription Registry

The Danish National Prescription Registry contains data on all prescription drugs dispensed to Danish citizens since 1995.[24] The data include the dispensed substance, brand name and quantity of the drug, date of dispensing, age and sex of the drug user, and identifiers for the prescribing physician and the dispensing pharmacy. While the DAMD gathers data on prescriptions issued by GPs, the Danish National Prescription Registry gathers data on all prescriptions dispensed, regardless of whether they were prescribed by GPs or specialists. Because this data source is more complete (including prescriptions from GPs and specialists) and does not include prescriptions that were issued but not dispensed (decreasing misclassification of exposure), we will identify medication use from this source.

6.1.3 Danish Person Registry

The Danish Person Registry contains data on vital status (dates of birth and death where appropriate) and migrations in and out of Denmark, thus rendering it possible to censor follow-up appropriately.

6.1.4 Taxation Registry

The Taxation Registry will be used a source of information about socioeconomic status at the individual level. In the Taxation Registry, disposable income is defined as income for a single family member after taxation and adjustment for the number of family members (http://www.dst.dk/en.aspx). For this study, subjects will be categorized on the basis of quartiles of disposable income at baseline into low (first quartile), medium (second and third quartile), and high (fourth quartile) income categories.[25]

6.1.5 The Cause of Death Registry

The Cause of Death Registry collects information on the underlying and contributing causes of death of all residents of Denmark since 1875. Data are retrieved from death certificates, which are completed by physicians. The physician in charge of the patient at the time of death is required to report the cause of death.[26] For persons who are found dead out of a hospital, their GP completes the death certificate, based on what is known about the patient's medical history. If an autopsy is performed, new diagnoses may be added to the death certificate.

6.1.6 Danish Cancer Registry

The Danish Cancer Registry is population based and contains records of all incidences of new malignant neoplasms in the Danish population from 1943. Reporting to the Danish Cancer Registry has been mandatory since 1987.[27] From 2004, reporting has been mediated via the National Patient Registry: when a cancer is entered in The Danish National Registry of Patients, the Danish Cancer Registry is automatically

notified. Information in the Danish Cancer Registry is cross-referenced against several sources (e.g., the Danish Pathology Registry, the Cause of Death Registry) to ensure completeness and remove duplicates. Additional information regarding, for example, mode of diagnosis or stage at diagnosis, is often requested. Less than 1% of cases in the Danish Cancer Registry are based solely on information from death certificates. Finally, there is an internal validity check of consistency, which may occasionally trigger requests for new information[28] For the majority of cancer groups, more than 90% of the tumors were histologically verified, including the major groups such as breast cancer, lung cancer, melanoma, and colon cancer. More information is provided in Section 6.6.3.2 on ascertainment of Neoplasm Endpoints.

6.2 Study Design Summary

Cohorts of patients who receive drugs used in the treatment of OAB will be drawn from the population during the study period of January 1, 2004, through December 31, 2012. The characteristics of the patients belonging to the overall cohort and to each cohort of new users of individual OAB medications will be described. The information available in the database on the major risk factors for CV endpoints and neoplasms that could act as potential confounders will be described, and the incidence rates of the endpoints in new users of the drugs of interest will be estimated.

6.3 Study Population

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

- Have at least 12 months of continuous residence in Denmark (thereby providing medical and prescription history data) before the first prescription or dispensing of an OAB drug of interest.
  - For most covariates, 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 measures of health care utilization.
- Have a first recorded prescription or dispensing for oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine.
- Be aged 18 years or older at the time of first prescription 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.
- Had a diagnosis of human immunodeficiency virus (HIV) infection.

The latter exclusion criterion was included in the present protocol for consistency with parts of the program that use other data sources, because it is expected that the diagnosis of HIV would modify provision of the patients' health care in such a manner that health care data would no longer be captured in those data sources. In the Danish

Data Resources, health care use of subjects with a diagnosis of HIV continues to be captured after diagnosis.

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 FDA *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets*[29]

A *new user* of any drug of interest will be a patient who receives a first prescription or dispensing for any OAB drug during the study period without a prescription or 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.

6.4 Follow-up

Follow-up of eligible subjects will start on the date of the first prescription for 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
- Death
- Emigration
- Diagnosis of human immunodeficiency virus (HIV) infection
- For all cancer analyses (for both composite and individual cancer endpoints), the first incident targeted cancer is considered to be the event 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.

6.5 Time at Risk and Exposure

6.5.1 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 be defined as described in the following paragraph. Recent use will include the first 60 days after current use, and past use will include person-time of the end of recent use.

The Danish National Prescription Registry does not hold data on the dosing instruction, and the prescription's period of usage may therefore not be inferred directly from the information available. Instead, prescriptions will be assigned a period of usage based on the dispensed quantity and a calculated average of daily use, specific for each substance. The calculated average of daily use can be computed as the ratio between dispensed quantity and the time until the next prescription for all prescriptions that are not last in a treatment episode. The sequences of prescriptions that belong to the same treatment episodes will be identified by the waiting-time approach[30]

6.5.2 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 prescription 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 prescription within the previous year for the study drug to which a subject is accruing person-time, and past use will be defined as more than 1 year since the most recent prescription was issued).
- Further description of the exposure groups of interest is provided in the data analysis section. Cumulative exposure to study drugs will be defined, according to the days of supply of each prescription where possible, 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 dispensing information recorded in the database.

Patients who enter the OAB drug–exposed cohorts will be considered “ever exposed” to OAB drugs. For the construction of user cohorts for single OAB medications, patients who enter the cohort of exposure to OAB drug A will be considered “ever exposed” to OAB drug A. Patients in the OAB drug A cohort who subsequently begin treatment with OAB drug B will have their person-time in the OAB drug A cohort censored at that time, and from the date of the first prescription of OAB drug B, their person-time will be entered into the cohort of those exposed to multiple OAB drugs (the multiple-exposure cohort).

6.6 Endpoints

6.6.1 Cardiovascular Endpoints

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

- AMI including out-of-hospital coronary heart disease deaths
- Stroke including out-of-hospital stroke-related deaths
- All-cause mortality
- CV mortality
  - Coronary heart disease death
  - Cerebrovascular disease death

The composite endpoint of major adverse cardiac events (MACE)—acute myocardial infarction, stroke, or cardiovascular mortality—will also be examined.

CV-related deaths that occur during hospitalization (e.g., a person admitted with an AMI who dies after 2 days) will be identified by the diagnostic codes for those hospitalizations. For persons who die outside a hospital, causes of death will be established by use of the Danish Cause of Death Registry, which is based on death certificates.[26] For persons who are found dead out of a hospital, their GP completes the death certificate, based on what is known about the patient’s medical history. If an autopsy is performed, new diagnoses may be added to the death certificate.

6.6.2 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 rates among both sexes in the US Surveillance, Epidemiology, and End Results (SEER) data, 2005-2009,[31] 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 an event 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 per 100,000 Person-years for Targeted Neoplasm Endpoints 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 & 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	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 on 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 on November 15, 2012.

Similar data are available for the Danish population in the NORDCAN collaboration (Table 2). Most rates are similar to rates from the US, but some cancers, including colon and rectum cancers, appear to have a higher incidence rate in Denmark. Some of these differences, e.g., colon, breast, and prostate cancers, may depend on different screening practices or on the fact that the Danish data are from a different period.

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

	All Ages		Aged ≥ 65 Years	
Type of Cancer	**Males**	**Females**	**Males**	**Females**
Colon and rectum	85.1	76.8	387	287,3
Pancreas	18.4	16.4	79.2	66.5
Lung and bronchus	84.9	77.9	384.3	278.4
Melanoma of the skin	35.8	37.4	108.4	68.7
Breast	—	158.9	—	379.8
Corpus uteri	—	27.5	—	88.1
Prostate	155.7	—	715.6	—
Urinary bladder	47.9	17.1	225.6	66.6
Kidney	16.9	9.4	55.1	30.5
Non-Hodgkin lymphoma	23.1	15.8	85.7	54.6
Total of the above	467.8	437.2	2,040.9	1,033.2
Any cancer except nonmelanoma skin cancer	647	599.5	2,632.1	1,785.1

Source: The NORDCAN Project. Available at: http://www-dep.iarc.fr/NORDCAN/English/frame.asp Accessed May 13, 2014.

6.6.3 Endpoint Ascertainment and Existing Validation Studies

6.6.3.1 Cardiovascular Endpoints

For CV endpoints, the Danish National Registry of Patients contains all cases of AMI and stroke that are diagnosed during hospitalizations. The Registry collects all information contained in the list of discharge diagnoses for each hospitalization of a Danish resident with a Central Person Registry number. Discharge diagnoses are entered in the patient record by specifically trained hospital physicians. In addition, fatal cases of AMI and stroke that occur out of a hospital are obtained from the National Cause of Death Registry. As entry of a cause of death is mandatory for every fatality that occurs in the country, the Registry can be considered to contain all fatal cases of AMI and stroke in Denmark. The validity of AMI diagnoses in the Danish National Registry of Patients has been assessed by four studies, and the validity of stroke by six studies. Details are provided in Section 4.2.3, and 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, with PPVs between 82% and 100% for AMI and 79% and 94% for stroke; the higher values being derived from the most recent studies.

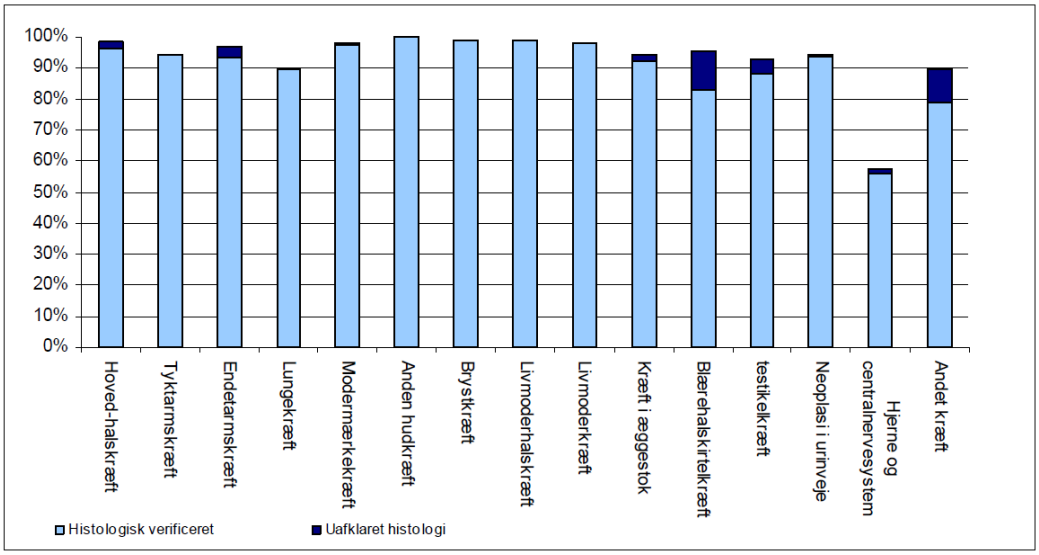
6.6.3.2 Neoplasm Endpoints

The source of data on cancer outcomes will be the Danish Cancer Registry, which is population based and contains records of all incident malignant neoplasms in the Danish population from 1943 onward. Reporting to the Danish Cancer Registry has been mandatory since 1987.[27] From 2004 onward, reporting has been mediated via the National Patient Registry, i.e., when a cancer is entered into the National Patient Registry either as a primary or nonprimary discharge diagnosis, the Danish Cancer Registry is automatically notified. The report is cross-referenced against known cancer reports to avoid duplicate reporting, and additional information regarding, for example, mode of diagnosis and stage at diagnosis, is requested. To ensure completeness, the Danish Cancer Registry is cross-referenced against the Danish Pathology Registry and the Cause of Death Registry to capture additional cases that have not been reported through the usual channels. Data for only a small proportion of cancer cases (less than 1%) is based solely on information from death certificates. Finally, there is an internal validity check of consistency, which may occasionally trigger requests for new information.[28]

The Danish National Health Board has analyzed the proportion of tumors that is histologically verified. In 2008, 87% of the tumors in the Danish Cancer Registry were histologically verified. For the majority of cancer groups, more than 90% of the tumors were histologically verified, including the major groups such as breast cancer, lung cancer, melanoma, and colon cancer (Figure 1). However, this does not imply that the cancer reports that are not verified histologically are not valid. For example, brain tumors are often diagnosed by imaging alone, for technical or clinical reasons. In addition, a small percentage of poorly differentiated cancers are not histologically classifiable.

Owing to the high coverage and validity of the Danish Cancer Registry and the diligence by which information is retrieved and cross-referenced, it is often regarded as gold standard in studies of cancer epidemiology in Denmark.[32,33]

Figure 1. Proportion of Reports in the Danish Cancer Registry Verified Histologically, by Category of Cancer Site



Note: The dark blue area represents tumors with poorly defined histology.

Cancer site categories, from right to left: andet kræft = second cancer; hjerne og centralnervesystem = brain and central nervous system; neoplasi i urinveje = urinary tract cancer; testikelkræft = testicular cancer; blærehalskirtelkræft = prostate cancer; kræft i æggestok = ovarian cancer; livmoderkræft = uterine cancer; livmoderhalskræft = cervical cancer; brystkræft = breast cancer; anden hudkræft = other skin cancers; modermærkekræft = melanoma; lungeKræft = lung cancer; endetarmskræft = rectal cancer; tyktarmskræft = colon cancer; hoved-halskræft = head and neck cancer.

The three studies that performed case validation against either the Danish Cancer Registry itself or the Danish National Registry of Patients, upon which it is based, are described in Section 4.2.3 and summarized in Appendix A. Positive predictive values are 98%-99%.

6.7 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 validation study, we will describe the study population.

The relevant confounding factors for CV disease, such as those outlined in Graham et al.[34] 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
- Use of OAB medications
- Health care utilization
- Smoking
- Obesity
- Alcohol/substance abuse
- Use of other medications (e.g., nitrates, other drugs used to treat angina, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEIs/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 frailty, will be used whenever possible. To address time-varying confounding, the status information for important confounders (such as health care utilization) will be updated during follow-up for the analyses described in the data analysis section.

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, menopause status, use of hormone-replacement therapy), all available information without time limitation will be used, although to estimate measures of health care utilization the 12-month period prior to the cohort entry date will be used. In addition, comparing the time of enrollment prior to cohort entry by exposure level might be useful for better understanding whether or not this decision may introduce a problem.

Table 3 describes the patient characteristic variables available in Danish data resources and their format.

Table 3. Description of Patient Characteristic Variables Available in the Danish Data Resources

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source
Birth or immigration, cohort entry, cohort exit, death or emigration dates	Date	Specific date	Central Person Registry
Cause of death	ICD-10 codes	Specific date	Cause of Death Registry
Duration of registration prior to cohort entry (days)	Number	Specific period	Central Person Registry, Danish National Prescription Registry
Duration of follow-up (days)	Number (date of cohort exit minus the date of cohort entry)	Specific period	Danish National Prescription Registry and others, depending on the reason for stopping follow-up
Demographics: age, sex	Age: numerical Sex: binary	Baseline	Central Person Registry
Socioeconomic characteristics: income	Categorical: specific categories depend on the data structure	Baseline (any time before the cohort entry date)	Taxation Registry
Genes: *BRCA1* and *BRCA2* mutations	—	—	This information will not be captured
Functional stage (capabilities for living a normal daily life); proxy for frailty	—	—	This information will not be captured
Smoking proxy	Binary	Baseline (any time before the cohort entry date)	Danish National Registry of Patients
Obesity	Binary	Baseline (any time before the cohort entry date)	Danish National Registry of Patients
Menopause	—	—	This information will not be captured
Hypertension	Binary	Baseline (any time before the cohort entry date)	Danish National Registry of Patients
Dyslipidemia	Binary	Baseline (any time before the cohort entry date)	Danish National Prescription Registry, based on prescribed treatment
History of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, pulmonary artery disease	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source
Diabetes without complications (diabetes with complications is included with the Charlson score)	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Family history of the individual cancers: Colon and rectum Pancreas Lung and bronchus Melanoma of the skin Breast (female) Corpus uteri Prostate Urinary bladder Kidney and renal pelvis Non-Hodgkin lymphoma	—	—	This information will not be captured
Comorbidities			
Alcohol abuse and related conditions	Binary	Baseline (any time before the cohort entry date) and time varying	The Danish National Registry of Patients, Danish Prescription Registry
Drug abuse	—	—	This information will not be captured
Comorbidities included in the Charlson Index	Each comorbidity: binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Renal impairment	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Dialysis	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Fractures	Binary	Time varying and proxy of frailty	The Danish National Registry of Patients
Gout	Binary	Baseline (any time before the cohort entry date)	Danish National Prescription Registry, based on prescribed treatment
Arthritis	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients – Specify disease entities
Overactive bladder	—	—	This information will not be captured

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source
Organ transplantation	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Polycystic ovary syndrome	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Endometrial polyps or other benign growths of the uterine lining	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Prescriptions Hormone-replacement therapy Tamoxifen use Thyroid hormone replacement Nitrates, digoxin, antidiabetic drugs, statins Non-aspirin NSAIDs Low-dose aspirin Antiplatelets (including aspirin in low doses) Immunosuppressive agents	Binary	Baseline (any time before the cohort entry date), time varying	Danish Prescription Registry All prescription drugs are fully covered; however, NSAIDs are available over the counter; 83% by volume (DDDs) is recorded in the Danish National Prescription Registry. Low-dose aspirin is also available over the counter; coverage in the Danish National Prescription Registry is 91%
Health services utilization			
Outpatient visits	—	—	This information will not be captured
Hospitalizations	Numerical	Baseline (12 months)	The Danish National Registry of Patients
Nursing home stay	—	—	This information will not be identified although data from nursing homes is captured in the registries
Sigmoidoscopies	Numerical	Baseline (12 months)	The Danish National Registry of Patients
Mammograms	Number	Time varying: per year, starting in the baseline period	The Danish National Registry of Patients

AMI = acute myocardial infarction; BRCA1 = breast cancer 1, early onset gene; BRCA2 = breast cancer 2, early onset; DDDs = defined daily doses; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; NSAIDs = nonsteroidal anti-inflammatory drugs.

7 STUDY SIZE

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

Table 4 shows the number of users of study drugs in Denmark in the period 2004 through 2012, by year. Solifenacin and tolterodine are the most frequently prescribed study drugs, as was reported in a drug utilization study conducted in the region of Odense, Denmark, for 2006.[7]

Table 4. Number of Users of Study Drugs, 2004-2012, Denmark

Drug Name, ATC Code	2004	2005	2006	2007	2008	2009	2010	2011	2012
Oxybutynin G04BD04	—	466	1,023	959	672	605	633	581	476
Tolterodine G04BD07	23,105	21,220	18,560	17,675	16,067	14,353	13,211	11,867	10,688
Solifenacin G04BD08	961	6,987	8,864	11,172	12,997	14,710	15,770	17,175	18,762
Trospium G04BD09	5,258	4,595	4,367	3,833	3,526	3,694	5,079	5,383	4,942
Darifenacin G04BD10	—	39	1,308	1,967	2,026	1,721	1,572	1,411	1,313
Fesoterodine G04BD11	—	—	—	—	1,009	3,532	4,569	5,668	6,112

ATC = Anatomical Therapeutic Chemical (classification system).

Note: Flavoxate and emepronium were not included in this list due to low utilization.

Source: Danish National Prescription Registry. Available at: www.medstat.dk. Accessed July 31, 2014

8 DATA MANAGEMENT

The six data sources that will be used in this study will be linked by using the Central Person Registry number, a unique identifier assigned to all Danish citizens since 1968 that encodes sex and date of birth. All linkage will occur within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes. Researchers can be authorized to access the data in Statistics Denmark. Confidentiality is ensured by several layers of password-protected sign-in, use of real-time password assigned by a remote token, exclusive use of de-identified data, and the fact that researchers cannot extract data from Statistics

Denmark, only the output of their analyses.[22] All analyses will be performed in Stata (StataCorp LP. College Station, Texas).

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following 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.

9 DATA ANALYSIS

9.1 Characterization of Users of OAB Medications

- Characterization of users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium) with respect to a series of selected covariates

9.2 Drug Prescription Patterns Description

- Description of the patterns of usage of OAB medications, including dose, duration of treatment, drug switching, and use of medications as add-on therapy

9.3 Validation of the Endpoints and Confounders

In the Danish 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 is available, such as age, sex, comorbidities, and medication use. Lifestyle characteristics, such as body mass index, may not be completely recorded. We will describe missingness in these variables in the full study population and among cohort members treated by sentinel doctors, whose information is considered best for research.

9.4 Cardiovascular Study

The cohort will be established using the CV inclusion and exclusion criteria.

Patient baseline characteristics will be assessed through analysis of data in the period prior to the cohort entry date. Baseline characteristics of interest will include age and sex, comorbidities related to OAB, other comorbidities, lifestyle factors and specific medication and health care services use. Comparisons of these baseline characteristics, including potential CV confounders, across drug-use groupings will be presented. De novo use and previous use of study drugs will be quantified.

Crude and age-sex-adjusted incidence (absolute risk) will be calculated for each outcome for the overall cohort of patients treated with study drugs and for each of the subcohorts of new users of individual drugs (current use of individual drugs in monotherapy or current use of combination therapy).

A variety of subgroup analyses will be conducted. Groups will include patients aged 65 years or more, individuals with risk factors for CV disease, and patients with established CV comorbidity. Analyses that are stratified by prior use of OAB drugs will be performed to address drug switching over the course of the study.

The impact of various intervals of time since exposure (e.g., recent use or past use) on the estimates of interest will be evaluated.

The incidence rate ratio of CV outcomes of each of the OAB medications compared with tolterodine, adjusted by all potential confounders, will be estimated.

The adjusted incidence rate ratio of each of the CV outcomes that are components of the MACE for each of the OAB medications will be calculated, and the homogeneity of the rate ratios of the components of the MACE endpoint will be evaluated.

9.5 Neoplasm Study

The cohort will be created using the neoplasm inclusion and exclusion criteria.

Patient baseline characteristics will be assessed through analysis of data in the period prior to the cohort entry date. Baseline characteristics of interest will include age and sex, comorbidities related to OAB, other comorbidities, lifestyle factors and specific medication and health care services use. Comparisons of these baseline characteristics, including potential cancer confounders, across drug-use groupings will be presented. De novo use and previous use of study medications will be quantified.

The occurrence of the composite cancer outcomes, by sex, will be estimated. The study report will summarize in each exposure category the number of enrolled patients, person-time, and frequency of first cancer events. Crude and age-standardized incidence (absolute rate) will be calculated for each of the sex-specific first composite cancer outcomes for the cohort of patients ever treated with any study drug, ever treated with each individual study drug, and ever treated with only each individual study drug.

Incidence rates for the first occurrence of the individual cancers will also be analyzed, although these estimates will be less precise than the incidence rates for the composite cancer endpoint. Incidence rates for individual cancers will be analyzed for males and females combined when appropriate. Patients who are not susceptible to developing an individual cancer type will not be included in the cancer type-specific analyses; for example, women who are known to have undergone prophylactic bilateral mastectomy

will not be included in an analysis of breast cancer alone, and women who are known to have had a hysterectomy will not be included in an analysis of uterine cancer alone.

If information on a particular covariate is available; patients will be assumed to have the factor only if there is evidence for its presence (i.e., values for covariates will not be considered missing and will not be imputed). The exception to this principle will be when "missing" is one of the possible values recorded for the variable (e.g., for smoking), in which case the value as listed within the database will be retained in the analysis as one of the possible values (e.g., smoking status will be "smoker," "nonsmoker," "former smoker," or "missing").

Additional details of the statistical analyses will be described in the statistical analysis plan.

10 QUALITY ASSURANCE

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the statistical analysis plan, abstraction forms, and study reports will undergo quality-control review and senior scientific review. Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)*.[4] The EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-Authorisation Safety Studies*, echoes this approach.[35]

11 STRENGTHS AND LIMITATIONS

The main strength of this study is that it utilizes databases covering the entire Danish population, with full capture and follow-up of everybody born in or immigrated into Denmark. The availability of nationwide databases on demographics, health status, and health care use make Denmark a highly attractive resource for pharmacoepidemiologic studies. All inhabitants of Denmark are followed from birth or immigration until either death or emigration, leading to a very low turnover and extremely good follow-up for essentially the entire lifetime of all cohort members. Exposures to OAB drugs and other prescription medications dispensed are virtually completely available for all inhabitants through the Danish National Prescription Registry, and all medical events that lead to inpatient or outpatient hospital care, all malignancies, and causes of death are retrieved from national registries that have been well validated tor accuracy and completeness of

data.[22] Next to the compete follow-up of nationwide cohorts, the presence of complete and accurate information on exposure and outcome are important strengths of this study.

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, hypertension, obesity, and other lifestyle factors. Data from the sentinel doctors in the DAMD, covering about 20% of the Danish population, and found to be generally representative of the entire Danish population[36] will be used to assess the distribution of these covariates in the national cohorts of OAB users. As this database contains GP data recorded during routine clinical practice, information on many covariates will necessarily be incomplete.

For a number of covariates, proxies will be used to infer their presence among 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.

12 PROTECTION OF HUMAN SUBJECTS

According to Danish law, register studies that do not entail contact with study subjects are exempt from review by an ethics board.[22] However, the study must be approved by the National Health Board, the Danish Data Protections Agency, and the steering group of the DAMD. These approvals will be sought by the University of Southern Denmark. 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.

13 OTHER GOOD SCIENTIFIC PRACTICE

The study will be conducted in accordance with the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,[4] the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*[37] 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 Sets*.[29] The ENCePP *Checklist for Study Protocols*[37] will be completed, and the study will be registered in the ENCePP study registry.[38]

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*[39] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII: Post-Authorisation Safety Studies*[35] and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012.[40]

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."*[14]

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 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."*[41]

Module VIII – Post-Authorisation Safety Studies, of the same document echoes this approach.[35] 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 milestones previously described.

SDU and RTI Health Solutions are granted independent publication rights in line with the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,[4] ENCePP code of conduct,[5] and the International Committee of Medical Journal Editors *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*.[6] 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[42] will be followed for study reporting.

16 PROPOSED RESOURCES TO CONDUCT THE STUDY

The project will be led by an epidemiologist at the professor level who will oversee the implementation of the project and documents and will be in charge of communication with research partners and Astellas. 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, analyses of data, and study results reports, with the aid of a senior statistician. Programming written by one programmer will be independently reviewed by a different programmer.

17 AMENDMENTS

Table 5. Summary of Amendments and Updates

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
2.0	February 23, 2015	Section 18, Data Sources	Unavailability of GP Database	GP Database not available during study period.
		Section 6.4, Follow-up; Section 6.6.2, Neoplasm Endpoints; Section 6.7, Potential Confounding Factors; and Section 9, Data Analysis	Refined definition for end of follow-up of neoplasm endpoints	Clarified that only occurrence of the first study neoplasms is considered as the endpoint; occurrence of any neoplasm determines end of follow-up, and a subject can experience first a CV endpoint and then a neoplasm endpoint

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
1.0	August 15, 2014	This was the original protocol		

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19 APPENDIX A. VALIDATION STUDIES CONDUCTED IN THE DANISH DATA RESOURCES

Table 6. Validation Studies of Myocardial Infarction Diagnoses in Denmark

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Coloma et al[10] 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 database before inclusion in cohort	Previous history of heart disease	100%
Joensen et al[11] 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 or Aarhus Not registered with a diagnosis of cancer at cohort entry	Diagnosed with ACS before cohort entry	81.9% (79.5%-84.2%)
Bjerrum et al[12] 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 et al[13] 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 one of 11 municipalities around Glostrup County Hospital in the western suburbs of Copenhagen	Hospitalization for AMI within 28 days prior to event or AMI as the underlying cause of death	93.6%

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

Table 7. Validation Studies of Stroke Diagnoses in Denmark

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Wildenschild et al[14] 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	Aged ≥ 18 years old	Subarachnoid haemorrhage	79%
Krarup et al[15] 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	Rater 1: 80.5% (73.6%-86.3%) Rater 2: 86.0% (79.7%-90.9%)
Johnsen et al[16] 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	Aged 50-64 years at cohort entry. Resident in urban area of Copenhagen or Aarhus Not registered with a diagnosis of cancer at cohort entry	Before enrollment, hospitalized with cardiovascular disease, i.e., stroke, TIA, ischemic heart disease, or peripheral arteriosclerosis	79.3% (74.9%-83.3%)
Gaist et al[17] Risk of subarachnoid haemorrhage in first degree relatives of patients with subarachnoid haemorrhage: 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 hospital with less than 10 registered patients in the study period	SAH: 93% (85%-98%); patients discharged from neurosurgery wards
Bak et al[18] 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%)
Østergaard[43] et al. Discontinuation of antiplatelet treatment and risk of recurrent stroke and all-cause death: a cohort study. Submitted for publication in 2014.	2007-2011	Participants in the National Indicator Project (NIP). Discharged with a stroke diagnosis from a hospital in the Southern Denmark region	Past stroke diagnosis, use of warfarin	94% (87.4%-97.8%)

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

Table 8. Validity of Cancer Diagnoses in the Danish Cancer Registry

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value and Sensitivity
Jensen et al[19] Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. Eur J Cancer Prev. 2002 Aug;11(4):359-64	1983-1989	Female inhabitants in the county of Aarhus with breast cancer diagnosed in the period January 1, 1983, to December 31, 1989	Patients known from death certificate only Patients with history of cancer Patients without histopathological diagnosis	PPV: 99% Sensitivity: 100%
Thorsteinsson et al[20] Completeness and validity of registration of childhood CNS tumours in the Danish Cancer Registry. Ugeskrift for Læger 2005;167(40):3782-3785. (In Danish)	1980-1996	Inhabitant in Denmark and aged 0-14 years at time of diagnosis	—	PPV: 98% Sensitivity: 97.9%
Osterlind and Jensen[21] Evaluation of cancer registration in Denmark in 1977. Preliminary evaluation of cancer registration by the Cancer Register and the National Patient Register. Ugeskrift for Læger 1985;147:2483-8. [Article in Danish]	1977	Registered in either DCR or DNPR with cancer diagnosis in 1977	—	Sensitivity: 94%

CNS = central nervous system; DCR = the Danish Cancer Register; DNPR = the Danish National Patient Register.; PPV = positive predictive value.