Title	Post-authorization Safety Study Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder: Core Common Protocol Protocol No. [178-CL-113]
Study identifier / Protocol Number	*EU PAS register number:* To be registered prior to data collection start
Protocol version & date of last version of protocol	Version: 7.0, Incorporating Substantial Amendments 1, 2, and 3 Date: 27 June 2016
Active substance	Mirabegron
Medicinal product	Betmiga (EU) Myrbetriq (US)
Product reference	NDA number 202611 EU/1/12/809/001-018
Procedure number	EMEA/H/C/002388
Marketing authorization holder(s)	Astellas Pharma Global Development, Inc.
Joint PASS	☐ Yes ☒ No

Research question and objectives	The primary objectives of this study are: • To estimate and compare the incidence of sex-specific composite cancer endpoints (1 for men and 1 for women) among new users of mirabegron and new users of any comparator antimuscarinic medication used in the treatment of overactive bladder (OAB), (referred to as 'antimuscarinic medications' throughout), stratified into categories of cancers that occur up to 1 year following the start of treatment, and those that occur more than 1 year following the start of treatment. • Repeat the analysis described above, restricted to patients ages 65 years and older. • To estimate and compare the incidence of the 10 individual sex-specific cancers included in the composite cancer endpoints among new users of mirabegron and new users of any comparator antimuscarinic medication, stratified into categories of cancers that occur up to 1 year following the start of treatment, and those that occur more than 1 year following the start of treatment. For both primary objectives, sensitivity analyses to examine protopathic bias will be conducted by estimating and comparing the incidence in post-treatment initiation intervals: 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, >= 24 months. A series of secondary objectives will be evaluated for the sex-specific composite outcomes. • To estimate and compare the sex-specific composite outcomes with the following modifications: o Stratify by new user status (i.e., naïve new users vs non-naïve new users). o Exclude immunocompromised patients. o Censor person-time when a patient switches from antimuscarinic treatment to mirabegron. • To estimate and compare the effect of cumulative exposure in tertiles of mirabegron cumulative dose relative to tertiles of antimuscarinic cumulative dose and within mirabegron exposure across tertiles of mirabegron cumulative dose.

Countries of study	United Kingdom, United States (2 data sources), Denmark, and Sweden
Number of Sites or Data Sources	5 research partners (each focusing on different data sources)
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2 LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

ATC	Anatomical Therapeutic Chemical
BRCA	Breast Cancer Gene
BRCA1	Breast Cancer 1, Early Onset Gene
BRCA2	Breast Cancer 2, Early Onset Gene
CI	Confidence Interval
CDR	Cause of Death Register
CHI	Comprehensive Health Insights
CPE	Centre for Pharmacoepidemiology
CPR	Central Person Registry
CPRD	Clinical Practice Research Datalink
DAMD	Danish General Practice Database
DDD	Defined Daily Dose
DNPR	Danish National Patient Register
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GOLD	General Practitioner data
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GPRD	General Practice Research Database; now the CPRD
GVP	Good Pharmacovigilance Practices
HES	Hospital Episode Statistics
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICD-10 CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-O-2	International Classification of Diseases for Oncology, Second Edition
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
ISAC	Independent Scientific Advisory Committee

ISPE	International Society for Pharmacoepidemiology
KI	Karolinska Institute
MHRA	Medicines and Health Care Products Regulatory Agency
NCDR	National Cancer Data Repository
NDL	No such data linkages
NMSC	Non-Melanoma Skin Cancer
NPR	National Patient Register
NPV	Negative Predictive Value
NSCLC	Non–Small Cell Lung Cancer
OAB	Overactive Bladder
ONS	Office for National Statistics
ORD	Optum Research Database
PASS	Post Authorization Safety Study
PB	Privacy Board
PDR	Prescribed Drug Register
PHIVE	Protected Health Information and Vendor Ethics Committee
PMR	Post Marketing Requirement
PPV	Positive Predictive Value
PS	Propensity Score
RR	Relative Risk
RTI-HS	RTI Health Solutions, a business unit of RTI International
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Swedish Cancer Register
SDU	University of Southern Denmark
SEER	Surveillance, Epidemiology and End Results Program
SIR	Standardized Incidence Rate
SOP	Standard Operating Procedure
UK	United Kingdom

List of main key terms unique in the study protocol

Terms	**Definition of terms**
New users	Patients who receives a prescription or dispensing for mirabegron or any specific antimuscarinic medication during the study period without a prescription or dispensing for the same medication in the previous 12 months. This definition permits patients to either be **naïve new users** or **non-naïve new users** depending on whether they had a prescription or dispensing for another overactive bladder (OAB) medication in the previous 12 months.
Naïve new users	Patients with a new prescription/dispensing of an OAB medication (mirabegron or an antimuscarinic medication) without any OAB medication prescriptions/dispensings during the baseline period.
Non-naïve new users	Patients with a new prescription/dispensing of an OAB medication (mirabegron or an antimuscarinic) who have a prescription/dispensing for some other OAB medication during the baseline period.

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4 SYNOPSIS

Date and Version # of Protocol Synopsis: 27 Jun 2016, Version 7.0

Sponsor: Astellas Pharma Global Development, Inc.

Protocol Number ISN: 178-CL-113

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

Name of Assessed Drug(s):

Mirabegron, Betmiga (EU), Myrbetriq (US)

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

Check One below:

☒ Mandated Study - US Food and Drug Administration

☐ Non-mandated Study

Check One below:

☐ Primary data collection

☒ Secondary data collection

☐ Mix of primary and secondary data collection

Check One below:

☒ Post-authorization safety study (PASS)

☐ Post-authorization efficacy study (PAES)

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

☐ *Other

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

Title of Study:

Post-authorization Safety Study
Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder

Guide to FDA reviewers

This amended protocol (version number 7.0) addresses key requests arising from discussion with the FDA during the Mirabegron post marketing requirement/post approval safety study (PMR/PASS) Type C meeting held on 21 March 2016, and the associated meeting minutes. The following themes have been covered:

1. The protocol has been reformatted using the EMA template for consistency across the 178-CL-114 common Core protocol and site-specific protocols.
2. The primary interim analysis is based on 3 main databases, defined as those that are linked to cancer registers (Danish National Databases, Swedish National Databases and Clinical Practice Research Datalink (CPRD)-linked). Additional interim analyses will be provided that will also include the complementary data sources, defined as the 3 unlinked sources – CPRD (unlinked), Optum Research Database (ORD) and Humana. (Section 9.7.2.1)
3. For the final report, full adjudication of cancer cases in the unlinked databases (CPRD-unlinked, ORD, Humana) will be undertaken, where administrative permissions are allowed. There is no distinction between primary and complementary analysis in the final study analysis and report. (Section 9.7.2.2)
4. More sensitive claims-based algorithms for identification of potential cases for adjudication have been described. (Section 9.1.1)
5. Methods to address generalizability of study results have been added. (Section 9.7.2.3)
6. An assessment of the consequences of the loss of access to the Danish general practitioner database (DAMD) has been included. (Section 9.4.3)
7. Measurement and selection of covariates (i.e., use of proxies and bias analysis) is reviewed. (Section 9.3.2)
8. Clarification of the definition of new users (naïve new users vs non-naïve new users) has been provided. (Section 9.1)
9. A description of methods for undertaking propensity score (PS) matching and meta-analyses has been included. (Section 9.7.2)

Study Rationale and Background:

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 or 50 mg once daily, depending on country of use. During the development program of mirabegron, 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 1 of the 6 OAB 12-week phase 2/3 randomized double-blind studies (Study 178-CL-047), serious adverse events (SAEs) within the system organ class of neoplasms [benign, malignant, and unspecified (including cysts and polyps)] were observed to be numerically, but not statistically significantly 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 5 phase 2/3 studies of the same 12-week duration. This post authorization safety study (PASS, or post marketing requirement (PMR) in the US) is designed to generate additional evidence to help evaluate the results observed in the clinical trials. To implement the program, we selected data sources from 5 research centers. The investigators are from RTI Health Solutions (RTI-HS), Optum, University of Southern Denmark (SDU), Centre for Pharmacoepidemiology (CPE) at Karolinska Institute (KI), and Comprehensive Health Insights (CHI).

The study population will include patients observed in each of the 5 databases, providing a wide array of patient characteristics, drug utilization and medical practice patterns, which will enhance the generalizability of the study findings to the population of mirabegron users in real world practice, beyond clinical trials. In preparation for the conduct of this Core protocol (178-CL-113), database-specific validation studies[a] were done to validate outcome definitions and assess the suitability of each data source for the PASS. In general, the results of these validation studies were similar across the databases, with no observed increased risk for any cancer associated with exposure to individual antimuscarinic medications (mirabegron was not included in these validation studies). Nevertheless, generalizability of results in this study will be addressed by reporting medication use characteristics across exposure groups and by reporting sex-specific incidence rates stratified by age categories, along with available information on potential effect modifiers such as smoking.

Age-adjusted incidence rates were generally higher in males than in females for all study cancers that affect both sexes and were also consistently higher for ages 65 years and older. In all of the studies, there was a substantially elevated incidence rate of cancer (most notably bladder and prostate) in the first 6 months after cohort entry relative to the follow-up intervals more than 6 months after cohort entry. These findings are consistent with those seen to date in the mirabegron phase 2/3 clinical program, and, in the observational studies, suggest the presence of protopathic bias, which may occur

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

when a patient experiences symptoms related to cancer that are misinterpreted as OAB symptoms. Another type of bias, surveillance bias, may occur when patients treated with antimuscarinic OAB medications experience symptoms that prompt further diagnostic work-up that might uncover an existing cancer that would not otherwise have come to medical attention. Methods to reduce the effect of these biases have been incorporated into this Core protocol through the planned separate analyses of the period immediately after initiating OAB treatment, so this period is excluded from certain analyses (to address protopathic bias) and balancing comparisons for diagnostic testing at baseline and assessing diagnostic testing during follow-up (to address surveillance bias).

Planned Study Period:

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

Study Objectives:

The primary objectives of this study are:

- To estimate and compare the incidence of sex-specific composite cancer endpoints (1 for men and 1 for women) among new users of mirabegron and new users of any comparator antimuscarinic medication (as a group) used in the treatment of OAB (referred to as 'antimuscarinic medications' throughout), stratified into categories of cancers that occur up to 1 year following the start of treatment, and those that occur more than 1 year following the start of treatment.
- Repeat the analysis described above, restricted to patients ages 65 years and older.
- To estimate and compare the incidence of the 10 individual sex-specific cancers included in the composite cancer endpoints among new users of mirabegron and new users of any comparator antimuscarinic medication, stratified into categories of cancers that occur up to 1 year following the start of treatment, and those that occur more than 1 year following the start of treatment.

For both primary objectives, sensitivity analyses to examine protopathic bias will be conducted by estimating and comparing the incidence in post-treatment initiation intervals: 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, >= 24 months:

A series of secondary objectives will be evaluated for the sex-specific composite outcomes.

- To estimate and compare the sex-specific composite outcomes with the following modifications:
    - Stratify by new user status (i.e., naïve new users vs non-naïve new users).
    - Exclude immunocompromised patients.

  - Censor person-time when a patient switches from antimuscarinic treatment to mirabegron.

- To estimate and compare the effect of cumulative exposure in tertiles of mirabegron cumulative dose relative to tertiles of antimuscarinic cumulative dose and within mirabegron exposure across tertiles of mirabegron cumulative dose.

Data Sources:

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

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

Analyses will include data summaries from each of the 5 databases. However, due to FDA's concern about using case-identification algorithms in unlinked data sources, a modified strategy is proposed. For the interim report, the primary analyses will include only those databases linked to cancer registries. These main data sources will include the Danish National Database, Swedish National Databases as well as the CPRD-DL (linked) database. Unlinked databases will provide supporting evidence for the interim report. These complementary databases include the CPRD-unlinked (NDL), the ORD, and the Humana databases. Claims-based algorithms that were validated in the data source specific validation studies will be used for case identification. For the final report, we propose using all 5 data sources for the primary and secondary analyses since the study outcomes will be based on validated cases using physician interviews and medical chart adjudication. More sensitive case-identification algorithms will be used to identify potential cases prior to adjudication.

The inclusion of all 5 databases will increase study power and enhance generalizability by providing data from a wider variety of user populations.

Study Population:

The study population will consist of new users of medications used for the treatment of OAB. A new user of any drug of interest will be a patient who receives a prescription or dispensing for mirabegron or any antimuscarinic OAB drug during the study period without a prescription or dispensing for the same specific medication in the previous 12 months. This definition permits a person to either be a naïve new user or a non-naïve new user. Patients who have a prescription or dispensing for mirabegron observed prior to study entry (i.e., an earlier but ineligible period of mirabegron use) will be excluded.

Two study cohorts will be defined; 1 cohort will be comprised of new users of mirabegron, and 1 cohort will comprise new users of antimuscarinic medications used in the treatment of OAB, including oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine, as available in each data source. Both cohorts may include both treatment naïve new users and non-naïve new users, i.e., those switching to mirabegron from antimuscarinic treatments. For each patient, follow-up will start on the day following the first observed prescription for or dispensing of a drug of interest and will finish, at the earliest, the end of the study period, death, disenrollment from the data source, end of the time period for which validated endpoints are available, dispensing/prescription of non-tablet forms of antimuscarinic medications, or the occurrence of any cancer other than non-melanoma skin cancer (NMSC), including any of the 10 study cancers.

Study Size / Number of Patients:

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

The following accrual information is based on the time from first observed dispensing/prescription reported in Table 1. Through September 2015, there were 9,293 mirabegron initiators in the CPRD. Through June 2015, there were 9,951 mirabegron initiators in the Optum's ORD database including commercially insured and Medicare Advantage enrollees. From 2013-2015, there were 19,264 mirabegron initiators in the Danish National Database. Data on counts of new initiators are not currently available for the Swedish National Database, but the number of mirabegron incident users was 8,116 in 2013, increasing to 21,445 prevalent and incident users in 2014, and 28,417 in 2015. Through June 2015, there were 3,475 mirabegron initiators in Humana's database including commercially insured and Medicare Advantage enrollees.

Study Design Overview:

This will be a cohort study comparing the incidence of commonly occurring malignant neoplasms among new users of mirabegron and new users of any comparator antimuscarinic medication (as a group) used in the treatment of OAB. To provide a sufficiently large patient population within which to evaluate the safety of mirabegron, the study will be conducted within multiple databases. Each of these populations will be studied according to the same Core protocol, although operational details

will vary across sites due to the specifics of the data environments. In addition to data source-specific analyses, estimates obtained from all data sources will be analyzed using a meta-analysis approach.

Incidence rates for the following sex-specific composite cancer endpoints will be calculated:

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

The incidence of the 10 individual cancers included in the composite endpoints will also be estimated within each exposure cohort.

Potential cases identified in data sources unlinked to cancer registries (ORD, Humana, and the practices within CPRD that are not linkable to the National Cancer Data Repository (NCDR) and Hospital Episode Statistics (HES)), will be confirmed for the final report by obtaining and reviewing additional information from source medical records, with appropriate administrative approvals. Validation of cancer outcomes through examination of medical charts is not necessary in Sweden or Denmark as cases are identified in cancer registries with high sensitivity and specificity. The same applies to most cancer cases in the subset of CPRD practices that are linkable to the NCDR and HES.

Comparison of cancer incidence will be made between mirabegron follow-up time and antimuscarinic follow-up time. A range of potential confounders for this comparison of neoplasm endpoints will be addressed through propensity score (PS) matching and the outcomes will be modeled using Cox proportional hazards regression to address differences in follow-up time between the cohorts. Study results will be expressed as estimated hazard ratios (HRs) of each study outcome comparing mirabegron to the reference antimuscarinic medications, adjusted to account for the sequential nature of the analysis in the primary analysis of the sex-specific composite cancer endpoints.

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

Inclusion/Exclusion Criteria:

The study population will consist of new users of mirabegron and new users of antimuscarinic medications. New mirabegron users may be either OAB treatment naïve or non-naïve new users (a prior antimuscarinic medication user). A new antimuscarinic medication user may be either OAB treatment naïve or non-naïve (might have previously used a different antimuscarinic medication). All new mirabegron and new antimuscarinic medication users will be naïve with respect to mirabegron at time of index. Database-specific protocols will outline the codes used to identify the study medications.

Inclusion:

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

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

Exclusion:

Patients will be excluded if they:

- Have diagnosis codes for any of the 10 study cancers, or any cancer other than NMSC during all available time prior to the index initiation of mirabegron or antimuscarinic medication.
- In databases lacking a cancer register, have other evidence of cancer (cancer codes, procedures such as mastectomy, chemotherapy or other cancer related therapies) during all available time prior to the index initiation of mirabegron or antimuscarinic medication.
- Have a dispensing/prescription for mirabegron in the observed data prior to the index dispensing/prescription of mirabegron or an antimuscarinic medication.

Comparative Groups:

For all analyses, the comparisons will be made between PS-matched cohorts of new users of mirabegron and new users of antimuscarinic medications used for the treatment of OAB.

Patient Selection:

The probability of starting treatment with mirabegron relative to antimuscarinic medications, conditional on baseline covariates, will be estimated to create a PS. The cohorts will then be PS-matched at a ratio of 1 new user of mirabegron to up to 4 comparator antimuscarinic medication users.

Endpoints for Evaluation:

Primary:

The primary endpoints are the occurrence of sex-specific composite cancers. The cancers included in the composite endpoints are the 10 cancers, excluding NMSC, with the highest overall incidence rates in the general population (8 among males, 9 among females, with 7 overlapping between the sexes to make 10 cancer types overall). These malignancies are:

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

Each of the individual cancers included in the composite measures will be examined, separately by sex.

Independent Variables:

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

Statistical Methods:

Sample Size Justification:

Sample size estimates are based on matching each new user of mirabegron to up to 4 new users of antimuscarinic medications, separately for men and women. Based on current accrual counts from the 5 data sources (through 2015), the analyses of cancer outcomes on cohorts are anticipated to include at least 20,000 person-years of exposure to mirabegron from male subjects (with 80,000 person-years in the comparison cohort, based on 1:4 PS matching) and at least 60,000 person-years with exposure to mirabegron from female subjects (with 240,000 person-years in the comparison cohort). Interim analyses are anticipated to include approximately 50% of the final analysis person-years. To account for the conduct of an interim analysis, an adjustment will be made to the estimation of confidence

intervals (CIs) for the primary sex-specific outcomes. Specifically, an O'Brien-Fleming adaptation[3] indicates use of a 99.6% CI for the interim analysis and 95.2% CI for the final analysis. The final analysis should deliver an upper bound of the 95.2% CI of the HRs lower than 1.5 with a probability of approximately 90% when the true HR is 1. These estimates are based on an incidence rate of 407.7 per 100,000 person-years for any study endpoint for males and an incidence rate of 303.9 per 100,000 person-years for any study endpoint for females[4]. In the interim report, updated incidence rates and patient accrual number will provide information for an updated estimate of the sample size for the final report

Data Analysis:

Within each data source, patients' baseline characteristics will be determined through analysis of data available up to and including the cohort entry date. Baseline characteristics of interest will include demographic variables including age and sex, comorbidities related to OAB, other comorbidities, and specific medication and health care services use. All covariates at baseline will be evaluated based on all available information, except for the evaluation of health care utilization and concomitant medications which will only be based on the 12 months before cohort entry. Accounting for potential confounders will be performed by matching on a PS estimated from available covariates to balance cohorts with respect to those covariates. The list of potential confounding variables in each data source will be based on the availability of that covariate in the data source and will be provided in database-specific protocols. Cox proportional hazards regression models of the time from the day after cohort entry until the occurrence of an event or censoring will be built. Censoring occurs on the last day of cohort eligibility and events occur on the dates of diagnosis of events. Primary analysis results will be stratified into time periods before or after 1 year since index exposure. Study results will be expressed as estimated adjusted HRs of the study outcomes along with CIs, adjusted for interim examination of the primary analysis of the sex-specific composite cancer endpoints. The antimuscarinic medication initiators will comprise the comparator group, so the HR will express the relative occurrence of events among mirabegron follow-up to antimuscarinic follow-up.

A series of primary and secondary analyses will be done within each database and then meta-analyses will be performed pooled at an aggregate level across databases. Estimates based on all patients will be reported as will estimates based on patients age 65 years and older. Generalizability of study findings will be addressed by reporting medication use characteristics across exposure groups and by reporting relative incidence rates (as HRs), stratified by age categories and by sex, along with available information on potential effect modifiers such as smoking.

Safety:

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

Interim Analyses:

The interim report will include data summaries from each of the 5 databases. However, the main analyses in the interim report will include only those databases linked to cancer registries. These main data sources will include the CPRD-DL (linked) practices, the Danish National Databases and Swedish National Databases. Unlinked databases will provide supporting evidence and will include the CPRD-unlinked, the ORD, and the Humana databases. The interim report will include summaries of estimated days of exposure based on dispensing/prescription information within the mirabegron and antimuscarinic treatment cohorts, evaluation of baseline characteristics of the treatment cohorts (before and after PS matching), and estimates of the rates of sex-specific composite cancer and HRs for mirabegron relative to antimuscarinic medications. These results will allow for reassessment of study power for the final study.

Dissemination Plan:

For the interim and final reports, separate study reports will be prepared by all research groups and a combined report will also be prepared by a lead site. Study reports will be sent to the FDA.

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

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

4.1 Flow Charts

Figure 1 Study Design Overview

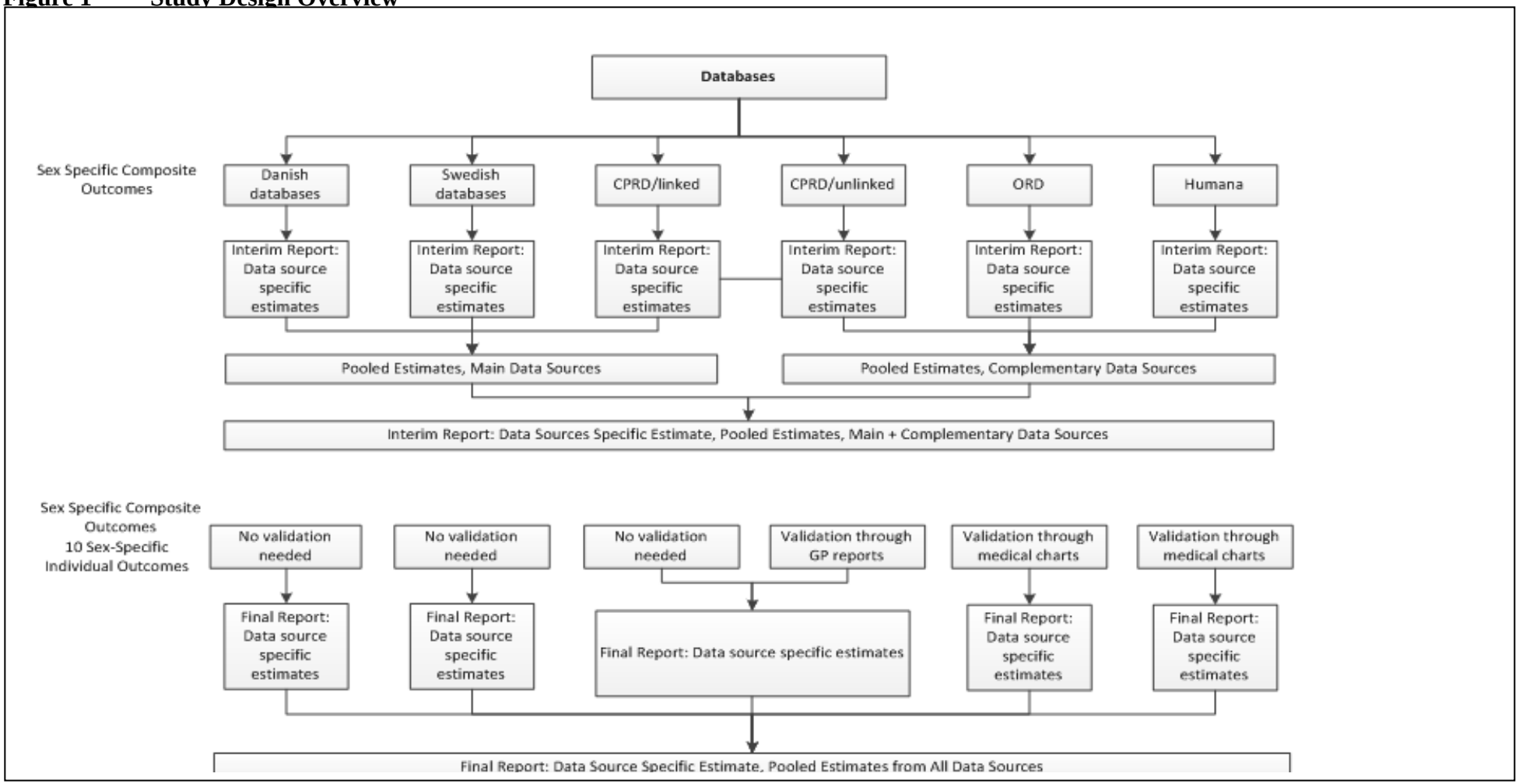
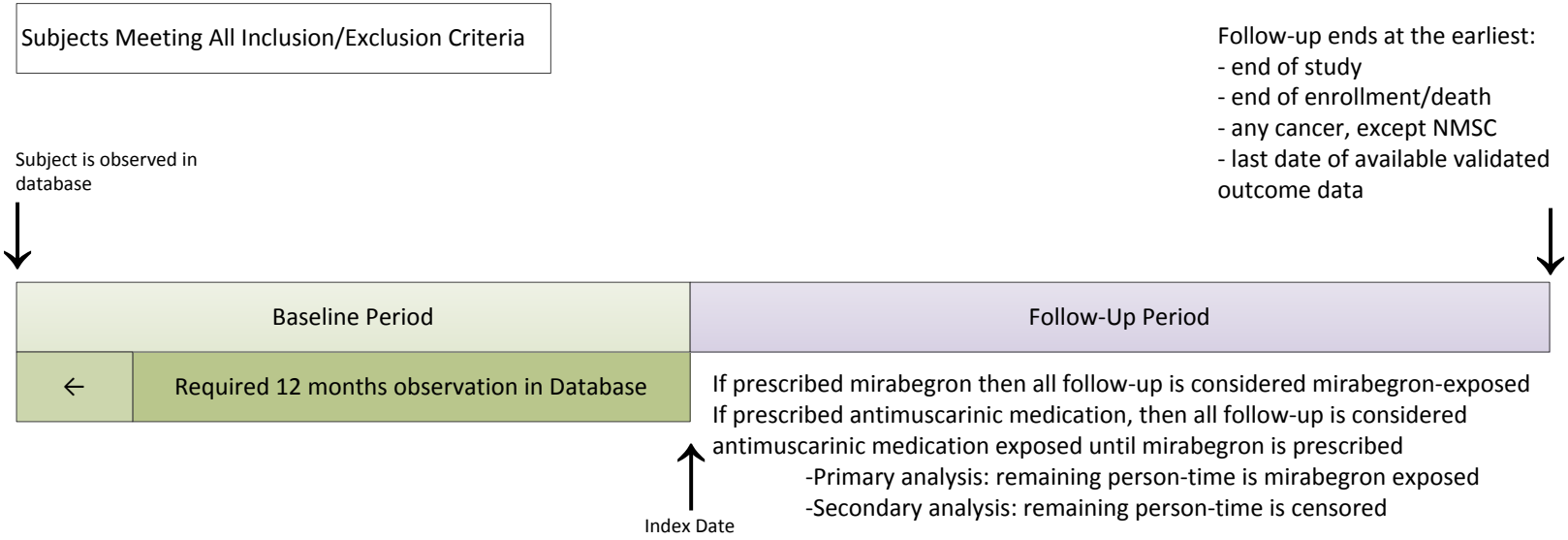


Figure 2 Schematic of Baseline and Follow-up Periods



4.2 Schedule of Assessments

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

	Dispensings/Prescriptions			Endpoints	
	Start	**Last Observed for Interim Report**	**Last Observed for Final Report**	**Last Observed for Interim Report**	**Last Observed for Final Report**
CPRD-linked	Feb 2013	June 2014	Dec 2016	June 2014	Dec 2016
CPRD-unlinked	Feb 2013	Nov 2016	Apr 2018	Nov 2016	Apr 2018
Optum	Oct 2012	Dec 2016	Dec 2017	Dec 2016	Dec 2017
Danish registers	Apr 2013	Jan 2017	Dec 2017	Dec 2016	Dec 2017
Swedish registers	May 2013	Dec 2015	Dec 2016	Dec 2015	Dec 2016
CHI-Humana	Nov 2012	Dec 2016	Dec 2017	Dec 2016	Dec 2017

5 AMENDMENTS AND UPDATES

Please note that this protocol has been transferred to the EMA template per the request of the FDA to improve readability of submissions, reduce errors, and preference for a unified table of contents from multiple contractors (as per 21 March 2016 FDA Type C meeting minutes). Due to differences in the section contents between protocol versions, we list only major changes rather than detailing section-by-section modifications.

Table 2 Amendments and Updates to Protocol 178-CL-113

Number	Date	Section number of study protocol	Reason
1. The timing and the purpose of the interim report have changed. Rather than providing a report of patient accrual numbers in June of 2018, an expanded report, including PS-matched HR for the sex-specific composite measures, will be provided in October of 2017. Type 1 error adjustments will be implemented.	June 2016	Synopsis, Section 6, Section 9.7.2	Implemented after recommendations made during the 21March2016 FDA Type C meeting.
2. For the interim report, designated Danish, Swedish and CPRD-linked as main data sources, with ORD, Humana and CPRD-unlinked as complementary	June 2016	Synopsis, Section 9.7.2	Implemented after recommendations made during the 21March2016 FDA Type C meeting.
3. For the final report, rather than rely on algorithms for outcome identification in the ORD, Humana and CPRD-unlinked, adjudication/validation will be completed, when permissions allow.	June 2016	Synopsis, Section 9.1.1, Section 9.7.2	Implemented after recommendations made during the 21March2016 FDA Type C meeting.
4. Methods for the meta-analysis have been revised and now conform with standard software to pool estimates across published studies.	June 2016	Synopsis, Section 9.7.2	Research Partners discussed methodology and available software for performing meta-analysis and concluded this approach is preferred because it is standardized, generalizable and replicable.
5. Separate descriptions of the CPRD-linked and CPRD-unlinked data have been provided.	June 2016	Synopsis, Section 9.4	Implemented after recommendations made during the 21March2016 FDA Type C meeting.

6 MILESTONES

Table 3 Milestones for Development and Conduct of Protocol 178-CL-113

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

7 RATIONALE AND BACKGROUND

During the clinical development program for mirabegron, a numerical imbalance was observed 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%) in a 52-week double-blind, randomized study. In addition, in 1 of the 6 overactive bladder (OAB) 12-week phase 2/3 randomized double-blind studies, serious adverse events (SAE) within the system organ class of neoplasms (benign, malignant, and unspecified (i.e., 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 5 phase 2/3 studies of the same 12-week duration.

The types of malignancies reported across all populations in the global phase 2/3 clinical program were consistent with the most commonly incident malignancies in the general population, with no predominance of any specific type. The malignancies that occurred in 2 or more mirabegron-treated patients were prostate cancer (4 events in 4 patients), breast cancer (3 events in 3 patients), lung cancer (4 events in 4 patients), non-melanoma skin cancer (NMSC) (15 events in 11 patients). New malignant events were reported most commonly during the first 6 months after the start of mirabegron treatment.[5]

On 28 June 2012, Astellas obtained marketing authorization in the US for mirabegron to treat OAB. The FDA issued a post marketing requirement (PMR) to evaluate cancer risks with mirabegron. This post authorization safety study (PASS) is designed to address this concern. This research effort will be organized as a program in multiple populations that will use data derived from electronic health care databases in the US and Europe. The studies performed in each database will follow the same Core protocol, although operational details will vary due to the specifics of the different data environments, therefore, site-specific protocols will be developed.

To prepare for a post marketing safety assessment of cancer risks associated with mirabegron use in 5 electronic health care databases, 5 validation studies were conducted. While initiators of mirabegron accumulated in each data source, research partners conducted validation studies among users of currently available antimuscarinic medications used for the treatment of OAB (referred to as ‘antimuscarinic medications’ throughout). These validation studies estimated rates of events and provided information regarding drug utilization patterns including duration of use, switching, and dose (where applicable) and addressed the gap in knowledge regarding the use and safety of currently available antimuscarinic medications outside the setting of clinical trials.

In general, results of these validation studies were similar across the databases, with no observed increase in the risk for any cancer associated with exposure to individual antimuscarinic medications. Age-adjusted incidence rates were generally higher for males than females for all study cancers that affect both sexes and were also consistently higher for ages 65 years and older. In all of the studies, there was a substantially elevated incidence rate of some cancers (most notably bladder and prostate) in the first 6 months after cohort entry relative to follow-up intervals more than 6 months after cohort

entry. These findings are consistent with those seen to date in the mirabegron phase 2/3 clinical program and suggest, in the observational studies, the presence of protopathic bias, which may occur when a patient experiences symptoms related to cancer symptoms that are misinterpreted as OAB symptoms. Another type of bias, surveillance bias, may occur when cancer symptoms in patients treated with antimuscarinic OAB medications experience symptoms that may prompt further diagnostic work-up that might uncover an existing cancer that would not otherwise have come to medical attention. Methods to reduce the effect of these biases have been incorporated into this Core protocol through the planned separate analyses of the period immediately after initiating OAB treatment, so this period is excluded from certain analyses (to address protopathic bias) and balancing comparisons for diagnostic testing at baseline and assessing diagnostic testing during follow-up (to address surveillance bias).

In the Clinical Practice Research Datalink (CPRD) study, standardized incidence rates (SIRs) were generally similar for patients ever-exposed to the specific study medications. The SIRs were higher in males than females for the composite outcome and for most types of cancer with the exception of melanoma and pancreatic cancer. The SIR for prostate cancer for patients ever-exposed to oxybutynin was higher than for patients ever-exposed to tolterodine among male patients.

In the ORD study, there was an elevated age-adjusted incidence rate ratio (IRR) for colon/rectal cancer among male patients for current exposure to tolterodine relative to current exposure to other antimuscarinic medications, while all other findings were consistent with unity or associated with relatively wide CIs.

In the Danish study, drug-specific SIRs were higher for breast and colon/rectal cancer among female patients and for colon/rectal and prostate cancer among male patients receiving fesoterodine. Lower SIRs were observed for tolterodine for each of these cancers and the associated CIs did not overlap between fesoterodine and tolterodine. Analyses by age group or for a subgroup of patients ≥ 65 years of age were not conducted in this study.

In the Swedish study, prostate, breast, and colorectal cancer were the 3 most common cancers, contributing 27%, 17%, and 16% of cases, respectively. No drug seemed to carry an increased risk of cancer. SIRs were generally similar across drug-use groups, and the drugs with the maximum and the minimum SIRs varied for the 10 study cancers. Analyses of cancer incidence rates by dose and by time since initiation of exposure showed that risk was higher with lower cumulative exposures and during early treatment, which is consistent with protopathic bias or surveillance bias. The effect on the composite cancer endpoint was driven by prostate and bladder cancers, the specific cancers that had the highest rates in the earliest periods.

In the Comprehensive Health Insights (CHI)-Humana study, oxybutynin was associated with a higher IRR for lung/bronchus cancer among female patients (with exposed person-time to any other OAB medication as reference). Among males in the CHI-Humana study, darifenacin and solifenacin had higher IRRs for the composite cancer endpoint, and solifenacin was associated with a higher IRR for colon/rectal and prostate cancer (with exposed person-time to any other OAB medication as reference). No other drug-specific, age-adjusted IRRs suggested elevated incidence.

Sections in the remainder of this document will start by addressing the common design features across data sources. Details regarding the implementation of these features in each data source will be provided in site-specific documentation.

8 RESEARCH QUESTION AND OBJECTIVES

The primary objectives of this program are:

- To estimate and compare the incidence of sex-specific composite cancer endpoints (1 for men and 1 for women) among new users of mirabegron and new users of any comparator antimuscarinic medication (as a group) used in the treatment of OAB, stratified into categories of cancers that occur up to 1 year following the start of treatment, and those that occur more than 1 year following the start of treatment.
- Repeat the analysis described above, restricted to patients aged 65 years and older.
- To estimate and compare the incidence of the 10 individual sex-specific cancers included in the composite cancer endpoints among new users of mirabegron and new users of any comparator antimuscarinic medication, stratified into categories of cancers that occur up to 1 year following the start of treatment, and those that occur more than 1 year following the start of treatment.

For both primary objectives, sensitivity analyses to examine protopathic bias will be conducted by estimating and comparing incidence in post-treatment initiation intervals: 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, >= 24 months.

A series of secondary objectives will be evaluated for the sex-specific composite outcomes.

- To estimate and compare the sex-specific composite outcomes with the following modifications:
    - Stratify by new user status (i.e., naïve new users vs non-naïve new users).
    - Exclude immunocompromised patients.
    - Censor person-time when a patient switches from antimuscarinic treatment to mirabegron.
- To estimate and compare the effect of cumulative exposure in tertiles of mirabegron cumulative dose relative to tertiles of antimuscarinic cumulative dose and within mirabegron exposure across tertiles of mirabegron cumulative dose.

9 RESEARCH METHODS

In the Core study, cohorts of patients who receive drugs used in the treatment of OAB will be identified from the US and European populations. The new-user design for the study medications will be adopted. The findings of the validation studies support the notion that the incidence of malignancies is similar among initiators of each of the antimuscarinic medications. Also, switching among the antimuscarinic medications may occur among patients with OAB, and the patient characteristics of initiators of each of the antimuscarinic medications are quite similar (with little evidence of channeling among antimuscarinic medications). Thus, the approach in this study is to select a comparison cohort comprised of a combination of new users of any antimuscarinic medication rather than to identify a specific comparator. The person-time contributed by the new users of antimuscarinic medications will provide an estimate of the "background" incidence of the endpoint cancers in the study population.

9.1 Study design

This is a cohort study including those exposed to mirabegron or antimuscarinic medications. Exposure will be based on prescription data and only new users will be included. A new user can be either a naïve new user (patients with a new prescription/dispensing of a medication for treatment of OAB (mirabegron or an antimuscarinic medication) without any OAB medication prescriptions/dispensings during the baseline period) or a non-naïve new user (patients with a new prescription/dispensing of an OAB medication (mirabegron or an antimuscarinic medication) who have a prescription/dispensing for some other OAB medication during the baseline period).

Each mirabegron user will be matched to up to 4 antimuscarinic medication users by propensity score (PS). Details of the variables included in the PS will be given in the statistical analysis plan (SAP).

9.1.1 Endpoints

The neoplasms observed in the mirabegron clinical development program were those that occur commonly in the general population. The primary outcomes are sex-specific composite of the 10 most commonly occurring malignancies in the US (excluding NMSC) based on those with the highest age-adjusted incidence rates among both sexes in the US Surveillance, Epidemiology and End Results (SEER) data, 2005-2009.[6] A composite measure of these 10 cancers fits with a general promoter hypothesis, unlike the inclusion of the four cancers noted in clinical trials. The incidence rates 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's lymphoma (19.6), kidney and renal pelvis (15.1), corpus uteri (12.6), and pancreas (12.1).

Because several of these cancers occur exclusively (or nearly exclusively) in males or females, the primary endpoints will be 2 composite sex-specific incidence rates defined as the occurrence of any of the individual sex-specific cancers as follows:

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

Each research partner has conducted validation studies of cancer endpoints in preparation for the Core protocols. As described in more detail in the subsections below, endpoints will be identified and ascertained differently in the different data sources.

All data sources that use International Classification of Disease (ICD) codes will use the list in Table 4. In Sweden, morphology codes (ICD-O-2,-3) will also be used. The definition of potential cases (e.g., the number and timing of observed codes) are provided in data source-specific sections, but the in situ codes will be used only for identifying patients who should be excluded prior to study cohort entry, not for case identification.

Table 4 International Classification of Disease (ICD) Diagnosis Codes to Identify Cancer Cases and/or Exclusion Criteria.

Condition	ICD-9 Cancer Codes	ICD-9 In Situ Codes	ICD-10 Cancer Codes	ICD-10 In Situ Codes
Bladder	188.xx	233.7	C67-	D09.0
Breast (female only)	174.xx	233.0	C50-	D05.XX
Colon/rectal	153.xx, 154.xx	230.3, 230.4	C18-,C19-,C20	D01.0, D01.2
Kidney and renal pelvis	189.0x, 189.1x	No specific code	C64-,C65-	No specific code
Lung and bronchus	162.xx	231.2	C34-	D02.2X
Melanoma	172.xx	No specific code	C43-	D03.XX
Non-Hodgkin's Lymphoma	200.xx, 202.xx	No specific code	C82-,C83-,C84-,C85-	No specific code
Pancreas (exocrine only)	157.0x-157.3x, 157.8x, 157.9x	No specific code	C25-	No specific code
Prostate (men only)	185.xx	233.4	C61	D07.5
Uterus (females only)	182.xx	233.2	C54-,C55-	D06.X

http://www.icd9data.com/2013/Volume1/, http://www.icd10data.com/ICD10CM/Codes, Accessed May 25, 2016

CPRD

Currently, approximately half of the total CPRD practices have consented to have their patient information linked, via a trusted third party, to other health care datasets. (It is expected that as the CPRD expands, there will be a further increase in the proportion of the covered population with linked information in these external data sources). Practices are therefore divided into those with data linkage (DL) to the National Cancer Data Repository (NCDR) and Hospital Episode Statistics (HES) and Office for National Statistics (ONS), and those with no such data linkage (NDL).

In HES and NCDR, tumors are coded using ICD-10 and correspond to those used in Sweden and Denmark above. Morphology of the tumors in NCDR is coded in ICD-10-O2 or -O3. General practice electronic medical records use Read codes. A full list of these codes will be reflected in the SAP.

For the final analysis in NDL (unlinked) practices, potential cases will be identified by the presence in their electronic medical records of the appropriate clinical Read codes. A questionnaire will be sent to their general practitioner (GP) to confirm/discard the case status. Remaining potential cases that could not be confirmed by means of questionnaires can have their patient profile (a chronological listing of all Read-coded entries -diagnoses, procedures, consultations, and others- and all prescription drug codes in a patient's general practitioner data (GOLD), except those for the study drugs, to preserve blindness in the case adjudication process) reviewed by a physician; if supportive evidence is found, they can be retained as "probable" cases; otherwise, they are not cases.

In DL (linked) practices, because additional cases may be found in the NCDR data that are not found in the GP records,[7] we will use 3 methods for screening and case validation within the DL practices.

1. Cases found after cohort entry in NCDR are automatically "valid" cases.
2. Cases found after cohort entry in HES are automatically "valid" cases
3. Potential cases not found after cohort entry in NCDR or HES and identified by the presence in their electronic medical records of the appropriate clinical Read codes, and will be validated through a questionnaire sent to their GP to confirm the case status. Cases confirmed through GP questionnaires will be considered "valid". Remaining potential cases that could not be confirmed by means of questionnaires will have their patient profile reviewed by a physician; if supportive evidence is found, they can be retained as "probable" cases. Otherwise, they are not cases.

For the interim analysis, in DL practices, cases found after cohort entry in NDCR, HES; and, in NDL practices, potential cases found searching electronic medical records for the appropriate clinical READ codes will be used in the analysis.

Optum Research Database (ORD) Claims Data

In the validation study performed in ORD in preparation for this program (Protocol 178-CL-115), cancer diagnoses were validated in a sample of the new users of OAB drugs. During that study period, ICD-10 coding had not yet been implemented in the US so only ICD-9 codes were used for case identification. In the validation study, patients were identified as potential cases if they had 2 or more claims with the corresponding ICD-9 diagnosis code in the follow-up period that were at least 30 days apart but not more than 90 days apart. The requirement that the pair of qualifying claims were within 90 days of each other was implemented to avoid including visits for ruling out cancer diagnoses as

valid cases. The date of the cancer outcome was assigned as the date of the first claim of the pair of qualifying claims. High positive predictive values (PPVs) were observed for most of the 10 cancer endpoints (range of 81% for lung cancer to 100% for breast cancer and 90% for a composite measure of all 10 cancers), but low negative predictive values (NPVs) were observed for the same 10 cancer outcomes (NPV range: 11% to 59%). This low NPV is a consequence of the initial pool of patients being those with at least 1 claim containing a cancer diagnosis, but not 2 diagnoses with the specified timing constraints so that it represents the NPV within a population that is enriched with cancer cases.

For the interim and final reports, the use of both ICD-9 and ICD-10 codes will be required. The validated ICD-9 algorithms will be used for the interim report, with modifications to incorporate diagnoses coded using ICD-10. Given FDA concerns about the performance of the algorithms used in the validation study, a more sensitive initial claims-based case identification method will be used to identify potential cases for adjudication for the final report. A higher sensitivity will be obtained by revising the timing between the 2 claims, requiring them to be 7 days apart (rather than 30) but retaining the upper limit for timing at not more than 90 days apart. This revision along with expanding the list of cancer codes to include carcinoma in situ will identify more potential cases, and these potential cases will be further adjudicated in the final report through medical records review conducted by clinicians blinded to drug exposure status.

Danish and Swedish National Databases

In the Danish and Swedish National Databases, endpoints will be ascertained via ICD-10 and ICD-O-3 (Sweden only) codes from cancer registries. No additional validation is needed.

Humana Claims Database

Cancer identification will be aligned with definitions used by Optum, taking into consideration the similarities of the US databases.

In the validation study on the Humana Database, the claims-based algorithms were defined using ICD-9-CM diagnosis codes. The PPV for any of the top 10 cancers of interest combined was 75.4% (95% CI: 70.9%, 80.0%); the PPV for the combined cancer endpoint was 82.3% (95% CI: 78.1%, 86.5%) when excluding cases with insufficient information to adjudicate case status based on medical record abstracts. PPV for the individual cancer algorithms ranged from 58.8% to 87.5% (and from 64.9% to 94.4% when excluding cases with insufficient information to adjudicate case status based on the abstracted medical records). PPV for cancer algorithms used to identify breast, kidney/renal, lung/bronchus, non-Hodgkin's lymphoma, pancreas, and uterine cancers all exceeded 80%. After excluding charts for which insufficient information necessary for case adjudication was obtained, PPVs for the algorithms used to identify these cancers exceeded 90%, with the exception of pancreatic cancer (PPV 86.7%). PPVs for algorithms used to identify bladder, colon/rectal, melanoma and prostate cancers were less than 80%. After excluding charts for which insufficient information necessary for case adjudication was obtained, PPV for the algorithm used to identify colon/rectal but not bladder, melanoma, and prostate cancer exceeded 80%. The NPV for any of the top 10 cancers combined was 95.7% (95% CI: 93.5%, 98.0%); the NPV for individual cancer algorithms ranged from 86.7% to 100.0%.

The case identification process described for the ORD will also be implemented within the Humana data. That is, for the interim and final reports, the use of both ICD-9 and ICD-10 codes will be required. The validated ICD-9 algorithms will be used for the interim report, with modification to incorporate diagnoses coded using ICD-10 codes. Given FDA concerns about the performance of the algorithms used in the validation study, a more sensitive initial claims-based case identification method will be used to identify potential cases for adjudication for the final report. A higher sensitivity will be obtained by revising the timing between the 2 claims, requiring them to be 7 days apart (rather than 30) but retaining the upper limit for timing at not more than 90 days apart. This revision along with expanding the list of cancer codes to include carcinoma in situ will identify more potential cases, and these potential cases will be further adjudicated in the final report through medical records review conducted by clinicians blinded to drug exposure status.

Table 5 and Table 6 provide a summary of validation studies conducted within the databases to be used in this study

Table 5 Validation of Incident Cancers Among GPRD and US Claims Data

Outcome (Reference)	Case Algorithm	Source of Cases	Gold Standard	Results
Incident breast cancer (Nattinger 2004)[a]	Breast cancer diagnosis code, lumpectomy or mastectomy, and radiation therapy; additional rules were applied to "low-likelihood cases"	US Medicare Claims (require diagnosis and specified procedures)	US SEER	Sensitivity: 80% PPV: 88%
Incident breast cancer (Gold 2007)[b]	Cases classified based on a statistical model with 19 claims-based variables	US Medicare claims, algorithm 1	US SEER	Sensitivity: 59%
	Breast cancer diagnosis code, lumpectomy or mastectomy, and radiation therapy; additional rules were applied to "low-likelihood cases"	US Medicare claims, algorithm 2	US SEER	Sensitivity: 80%-77%
	Model based on breast cancer diagnosis codes only	US Medicare claims, algorithm 3	US SEER	Sensitivity: 76%-74%

Outcome (Reference)	Case Algorithm	Source of Cases	Gold Standard	Results
Incident breast cancer (Rolnick 2004)[c]	At least 2 breast cancer diagnosis codes	HMO claims among HMOs associated with PE research	US SEER	Sensitivity: 92%-97% PPV: 83%-92%
Incident breast cancer (Koroukian 2003)[d]	Breast cancer diagnosis, lumpectomy, and/or mastectomy. If lumpectomy only, then radiation or chemotherapy was required.	Medicaid claims (at least 12-month enrollment)	US SEER	Sensitivity: 78% PPV: 85%
NSCLC (Ramsey 2009)[e]	At least 2 claims for diagnosis of NSCLC (results for a single claim are also reported but are not listed here)	HMO claims (Puget Sound)	US SEER	Sensitivity by insurance type; range obtained from stratification by days from diagnosis date Commercial insurance: 82%-99% Medicaid: 28%-50% Medicare: 79%-89%
Incident lymphoma (Setoguchi 2007)[f]	Four definitions were used for each cancer: Least specific based on >= 1 diagnosis code Most specific based on a diagnosis code and at least 1 treatment code	US Medicare claims	US state cancer registry	Sensitivity: 55%-89%, range by algorithm PPV: 35%-63%, range by algorithm

Outcome (Reference)	Case Algorithm	Source of Cases	Gold Standard	Results
Incident breast cancer (Setoguchi 2007)[f]	Four definitions were used for each cancer: Least specific based on >= 1 diagnosis code Most specific based on a diagnosis code and at least 1 treatment code	US Medicare claims	US state cancer registry	Sensitivity: 47%-87% PPV: 50%-82%
Incident lung cancer (Setoguchi 2007)[f]	Four definitions were used for each cancer: Least specific based on >= 1 diagnosis code Most specific based on a diagnosis code and at least 1 treatment code	US Medicare claims	US state cancer registry	Sensitivity: 56%-87% PPV: 45%-76%
Incident colorectal cancer (Setoguchi 2007)[f]	Four definitions were used for each cancer: Least specific based on >= 1 diagnosis code Most specific based on a diagnosis code and at least 1 treatment code	US Medicare claims	US state cancer registry	Sensitivity: 67%-88% PPV: 45%-71%
Incident lung cancer (Dregan 2012)[g]	Diagnosis code for lung cancer	GPRD	English Cancer Registry	PPV: 96%
Incident urinary tract cancer (Dregan 2012)[g]	Diagnosis code for urinary tract cancer	GPRD	English Cancer Registry	PPV: 92%
Incident colorectal cancer (Dregan 2012)[g]	Diagnosis code for colorectal cancer	GPRD	English Cancer Registry	PPV: 98%

Outcome (Reference)	Case Algorithm	Source of Cases	Gold Standard	Results
Incident cancers (individual and composite) (Mortimer, 2015)[h]	Medical Record Validation of Algorithms for 10 Types of Cancer Within a US Administrative Claims Database	ORD	Medical record adjudication	PPV: 81-100% for individual cancers, 90% (95% CI: 87-94%) for composite measure

GPRD=General Practice Research Database (not the Clinical Practice Research Datalink) ; HMO=health maintenance organization ;

NSCLC = non–small cell lung cancer; ORD=Optum Research Database; PPV = positive predictive value;

SEER = Surveillance, Epidemiology and End Results program (US National Cancer Institute).

a. Nattinger AB, Laud PW, Bajorunaite R, et al. An algorithm for the use of Medicare claims data to identify women with incident breast cancer. Health Serv Res. 2004; 39(6 Pt 1):1733-49.

b. Gold HT, Do HT. Evaluation of 3 algorithms to identify incident breast cancer in Medicare claims data. Health Serv Res. 2007; 42(5):2056-69.

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d. Koroukian SM, Cooper GS, Rimm AA. Ability of Medicaid claims data to identify incident cases of breast cancer in the Ohio Medicaid population. Health Serv Res. 2003; 38(3):947-60.

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Table 6 Validation Studies Conducted in the Danish and Swedish Cancer Registry

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value and Sensitivity
Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from 1 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 a history of cancer Patients without a histopathological diagnosis	PPV: 99% Sensitivity: 100%
Thorsteinsson R, Sørensen M, Jensen TL, Bernhardtsen TM, Gjerris F, Carstensen H, et al. [Central nervous system tumours in children. An evaluation of the completeness and validity of the Cancer Registry] [article in Danish]. Ugeskr Laeger. 2005 Oct 3; 167(40):3782-5.	1980-1996	Inhabitant in Denmark and aged 0-14 years at time of diagnosis	—	PPV: 98% Sensitivity: 97.9%
Østerlind A, Jensen OM. [Evaluation of cancer registration in Denmark in 1977. Preliminary evaluation of cancer registration by the Cancer Register and the National patient Register] [article in Danish]. Ugeskr Laeger. 1985 Jul 29; 147(31):2483-8.	1977	Registered with cancer diagnosis in 1977 in either the Danish Cancer Registry or the Danish National patient Registry	—	PPV: not estimated Sensitivity: 94%
Barlow L, Westergren K, Holmberg L, et al. The	1998	All malignant cancer cases (according to ICD-	After elimination	Underreporting of 3.7% of

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value and Sensitivity
completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009; 48:27-33.		10: C00-C96, except C77-C79) in the Hospital Discharge Register from 1998, irrespective of whether the cancer diagnoses were main or secondary. In total, there were 43,761 such discharges.	of reporting of multiple tumors and of multiple discharges for the same tumor, where the last record was kept for each tumor, there remained 42,010 combinations of individual and diagnostic-group	individuals with malignant disease in the Swedish Cancer Register for year 1998. 91.8% PPV for Hospital Discharge Register =test and Cancer Register ='gold standard'.

9.1.2 Comparative Groups

The probability of starting treatment with mirabegron relative to antimuscarinic medications, conditional on baseline covariates, will be estimated to create a PS. For all analyses, the comparisons will be made between PS-matched cohorts of new users of mirabegron and new users of antimuscarinic medications used for the treatment of OAB. Methods for matching are described in Section 9.7.2.1.

9.2 Setting

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

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

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

Investigators from the University of Southern Denmark will lead the work involving Danish data. In Denmark, the Danish health care system provides universal coverage to all Danish residents, approximately 5.6 million individuals in 2013. The centralized Civil Registration System in Denmark allows for personal identification of the entire Danish population through a unique identification number (CPR number). Use of CPR numbers ensures unambiguous record linkage between all

Danish registries, such as the Danish National Registry of patients, which provides data on all admissions to hospitals, the Danish National Prescription Database, the Danish Cancer Registry, and the Danish Registry of Causes of Death.

Investigators from the Centre for Pharmacoepidemiology (CPE), Karolinska Institute (KI) will lead work involving Swedish data. In Sweden, all residents are entitled to publicly financed health care covering the entire population, estimated to be 9.6 million in 2013. Many population-based health registries have been established with the use of the unique personal registration number. The personal registration number is given at birth or immigration to all Swedish residents and kept throughout life. In health care, the personal registration number is used for vital statistics and is also the unique identifier and key variable linking different registers. Information in the registers is recorded by current ICD, ICD-O/3, and/or Anatomical Therapeutic Chemical (ATC) codes. Data will be obtained from theTotal Population Register (with immigrations and emigrations), the National Patient Register (with inpatient and outpatient data), the Swedish Cancer Register, the Cause of Death Register, and the Swedish Prescribed Drug Register.

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

9.2.1 Selection of Study Population

The study population will consist of male and females at least 18 years old who are new users of medications used for the treatment of OAB. A new user of any drug of interest will be a patient who receives a prescription or dispensing for mirabegron or any antimuscarinic OAB drug during the study period without a prescription or dispensing for the same specific medication in the previous 12 months. Any patient with a prescription or dispensing of mirabegron use in the baseline period will be excluded, therefore, by definition, new mirabegron users may be either treatment naïve or non-naïve for antimuscarinic medications. A new antimuscarinic medication user is either naïve or has switched from another antimuscarinic medication. All new mirabegron and new antimuscarinic medication users will be naïve with respect to mirabegron at time of index. As the study is focusing on the evaluation of the safety of mirabegron relative to antimuscarinic medications, the study population will include all new users of mirabegron and antimuscarinic medications; an OAB diagnosis will not be required. Due to differences in the medication coding schemes used in the various databases involved in the study, the site-specific protocols will outline the codes used to identify the study medications in each database.

9.2.2 Inclusion

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

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

9.2.3 Exclusion

Patients with any of the following will be excluded:

- Have diagnosis codes for any of the 10 study cancers, or any cancer other than NMSC, during all available time prior to the index initiation of mirabegron or antimuscarinic medication.
- In databases lacking a cancer register, have other evidence of any cancer other than NMSC (e.g., cancer codes, procedures such as mastectomy, chemotherapy or other cancer related therapies) during all available time prior to the index initiation of mirabegron or antimuscarinic medication.
- Have a dispensing/prescription for mirabegron in the observed data prior to the index dispensing/prescription of mirabegron or an antimuscarinic medication.

9.2.4 Discontinuation Criteria (Censoring Criteria)

Follow-up of eligible patients will start on the day after the index prescription or dispensing for mirabegron or antimuscarinic (cohort entry date or date of subsequent switch to mirabegron). Follow-up for the composite cancer endpoints will finish at the earliest of the following dates:

- End of the study period.
- Last date of data with validated cancer outcomes within each of the data sources.
- Disenrollment from the data source (e.g., emigration, death).
- Occurrence of any cancer other than NMSC, including the 10 study cancers.
- Dispensing or prescription of a non-tablet types of antimuscarinic medication (due to the difficulty assigning person-time during use of syrups, patches, gels, or intravesical medications).

- For patients in the antimuscarinic cohort, initiation of mirabegron therapy (for some analyses only).

9.3 Variables

9.3.1 Exposure Definition and Measurement

Exposure to the study drugs mirabegron, oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine will be assessed using the prescriptions or dispensings as recorded in each database. Starting with the first day after the date of the index prescription or dispensing of mirabegron, all subsequent person-time will be classified as mirabegron-exposed until the end of follow-up (as defined in Section 9.2.4). Similarly, starting with the first day after the date of the index prescription or dispensing of an antimuscarinic medication, all subsequent person-time will be classified as antimuscarinic-exposed until the end of follow-up or an observed dispensing or prescription for mirabegron. Categorization of the subsequent person-time will be handled in 2 different ways, as describe in the Data Analysis section 9.7.2. If a patient is dispensed or prescribed mirabegron and antimuscarinic medication on the same day, all future person-time will be categorized as mirabegron-exposed, as that is the exposure of interest in this study.

Cumulative exposure to mirabegron or antimuscarinic medications will be defined according to the defined daily dose (DDD), defined by the World Health Organization as the assumed average maintenance dose per day for a drug that is used for its main indication.[8] In data sources without direct information on days supply, daily dose will be estimated by dividing the total amount of drug prescribed by the sum of the days between consecutive prescriptions or, for single prescriptions, from the number of DDDs of the supply (Danish and Swedish National Databases). In the case of missing values for the dose field, the dose will be estimated from descriptive analysis of the available recorded information (e.g., strength, number of units, amount of drug prescribed). Although details will vary based on the specific data source, exposure will be classified using drug exposure start date (day after the date of prescription or dispensing), days supply (depending on availability in the database), and dose. Details of these data source-specific calculations will be provided in site-specific documentation.

9.3.2 Covariates

In each data source, potential differences in cancer risk between users of mirabegron and users of antimuscarinic medications will be controlled for by evaluating and adjusting for a broad range of baseline characteristics. The list of pre-specified covariates in the study data sources is summarized in Table 7. These covariates will be included in the PS modeling process as well as additional variables in the Cox model after matching has occurred if imbalances remain. Factors include age, sex, geographic area of residence, characteristics that define elevated risk of malignancies (e.g., smoking for lung cancer and breast cancer gene (*BRCA)* mutations for breast cancer), relevant diagnoses related to OAB, use of mirabegron and antimuscarinic medications, health care utilization, smoking, obesity, diabetes, alcohol abuse/substance abuse, use of other medications (e.g., potent immunomodulators), and comorbidities (e.g., chronic obstructive pulmonary disease, forms of arthritis, renal impairment). In addition to these pre-defined covariates, empirically-identified

variables will also be considered. Confounders will be obtained directly or derived from within the baseline data in each data source when available. Otherwise, for variables not well-characterized in the source data, proxies will be used, and estimates from external sources may be used for context.

The other drugs potentially associated with increased or decreased cancer risk (e.g., unopposed estrogens, antineoplastic drugs, finasteride, thiazides, azathiorine) or drugs which may be used prophylactically (e.g., tamoxifen) are likely to be infrequently used at baseline among the study cohort (due to exclusion of patients with baseline evidence of cancer), and therefore are unlikely to be confounders for the sex-specific cancer outcomes. Use of non-steroidal anti-inflammatory drugs are associated with a decreased occurrence of colon cancer, and the use of these drugs is expected to be frequent (although incompletely captured due to over-the-counter availability). Methods for including these covariates in individual cancer-specific models, rather than in the overall PS, will be addressed in more detail in the SAP.

The covariate-capturing period, which may comprise multiple periods of coverage, will vary in duration for different covariates as some are intended to describe current health status while others aim at describing health history. For example, although only the 12-month period before cohort entry will be used to estimate health care utilization and concomitant medications, other potential covariates will be based on all available information before the cohort entry date (e.g., history of bilateral mastectomy, menopause status, use of hormone-replacement therapy). The covariate-capture periods will be outlined in detail in the common SAP. Drug use patterns differ between the US and Europe; therefore, the final choice of confounders may vary across data sources. However, common strategies to deal with confounding will be adopted across research sites and are described in the data analysis section. For each data source, a bias analysis[9] will be done to evaluate the potential effect of residual confounding by characteristics that are not well captured in that data source. This assessment will be performed prior to pooling estimates across data sources.

Within each data source, if information on a particular confounding variable is available, patients will be assumed not to have the factor if there is no evidence for its presence (i.e.,, values for confounder variables used in a given data source will not be considered missing). The only exception to this principle will be in the situation where “missing” is 1 of the possible values recorded for the variable (e.g., for smoking in the CPRD), in which case the value as listed within the data source will be retained in the analysis as 1 of the possible values (e.g., smoking status in the CPRD can be “smoker,” “non-smoker,” “former smoker,” or “missing”).

Table 7 Pre-specified Covariates for Inclusion in the Propensity Score Models and Availability by Data Source

Variable(s)	CPRD	ORD and Humana	Danish National Databases	Swedish National Databases
Age (continuous and age < 65 years)	Yes	Yes	Yes	Yes
Sex	Yes	Yes	Yes	Yes

Variable(s)	CPRD	ORD and Humana	Danish National Databases	Swedish National Databases
Geographic areas (site specific categories)	Yes	Yes	Yes	Yes
Use of medicines for OAB (mirabegron, any antimuscarinic medications, individual antimuscarinic medications)	Yes	Yes	Yes	Yes
Hormone-replacement therapy	Yes	Yes	Yes	Yes
Inflammatory bowel disease (ulcerative colitis and Crohn's disease)	Yes	Yes	Yes	Yes
Hypertension (diagnosis or medications)	Yes	Yes	Yes	Yes
Polycystic ovary syndrome	Yes	Yes	Yes	Yes
Endometrial polyps or other benign growths of the uterine lining	Yes	Yes	Yes	Yes
Diabetes (diagnosis or medications)	Yes	Yes	Yes	Yes
History of bilateral mastectomy	Yes	Yes	Yes	Yes
Number of hospitalizations (past 12 months, any in past 1 month)	Yes	Yes	Yes	Yes
Number of ER visits (past 12 months)	Yes	Yes	Yes	Not available
Number of outpatient physician office visits (not including labs, diagnostics, or other types of visits, i.e., physical therapy)	Yes	Yes	Yes	Yes
Number of sigmoidoscopies (past 12 months)	Yes	Yes	Yes	Yes
Number of colonoscopies (past 12 months)	Yes	Yes	Yes	Yes

Variable(s)	CPRD	ORD and Humana	Danish National Databases	Swedish National Databases
Number of mammograms (past 12 months)	Yes	Yes	Yes	Yes[a]
Immunomodulator medications (past 12 months)	Yes	Yes	Yes	Yes
Variables with limited availability				
Obesity (diagnosis codes, procedures, medications)	Limited	Limited	Limited	Limited
Tobacco use (smoking related diagnoses, smoking cessation medications, procedures)	Limited	Limited	Limited	Limited
Alcohol abuse/substance abuse	Limited	Limited	Limited	Limited
Menopause status	Limited	Limited	Limited	No
Radiation exposure (occupational and other)	Yes, based on codes (likely limited)	No	No	No
Family history of individual cancers	Yes, based on codes	No	No	No
BRCA1 and *BRCA2* mutations	Yes, based on codes	No	No	No

[a] There are screening programs in Sweden including all women above 40 years of age. The screening mammograms are not included in the register, only clinical mammograms are found in the register.

9.4 Data sources

9.4.1 Clinical Practice Research Datalink

CPRD, formerly known as the General Practice Research Database (GPRD), contains the information recorded by GPs as part of their routine clinical practice in the UK (http://www.cprd.com/intro.asp), in addition to linkage to certain other data sources. The CPRD covers approximately 8% of the UK population and includes approximately 5.1 million active users who are alive and currently contribute data to the database. Patients are representative of the whole UK population in terms of age and sex. The database includes approximately 900,000 individuals aged 65 years or older, of which 500,000 are women. Some research has been conducted on OAB treatments in the CPRD.[10]

The following sources of information are available in CPRD:

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

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

ONS Death data.

NCDR: The data consists of tumor level records submitted to ONS by the England Cancer Registries together with a further sub-set of data covering additional data fields required for analysis purposes. Tumors are coded using ICD-10 (topology) and ICD-10-O2 or -O3 (morphology) in data from all registries available in the ONS Core dataset.

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

CPRD data linkable (DL) population

A subset of specific general practices permit linkage to HES data, the ONS mortality data, and data from the NCDR. The potential cohort members are identified in GOLD and other data sources are used in addition to GOLD data to exclude patients who meet exclusion criteria, as necessary. Study outcomes are ascertained from general practice records in the CPRD and via linkage to external data sources—HES data, the ONS mortality data, and data from the NCDR.

CPRD not data linkable (NDL) population

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

9.4.2 Optum Research Database

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

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

The average length of enrollment in the ORD is approximately 2.4 years and varies considerably within subgroups; thus, eligibility criteria for a particular study can alter the follow-up available considerably. For example, older age groups have longer enrollment, with an average of almost 5 years for those over 50 years of age. Underlying information is geographically diverse across the US. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber identifiers, allowing longitudinal tracking of medication refill patterns and changes in medications. Medical claims or encounter data are collected from all available health care sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards.[11,12,13]

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

The Medicare Advantage members' claims were not included in the Optum validation study because Optum has only recently obtained approval for a process that provides access to medical charts for validation purposes within this population.

9.4.3 Danish National Databases

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

The Danish National Databases are population-based clinical databases on health care data that contain valuable information for epidemiologic research; they are linked with each other through the CPR personal identification number.[14] For the purpose of this study, we will use the following databases:

The Danish National Patient Register (DNPR) includes inpatient and outpatient visits to hospitals.[15] It provides data on all admissions to hospitals since January 1, 1977, and on visits to outpatient clinics and emergency departments since 1995. Diagnosis codes are registered by the discharging physician at the time of the hospital discharge. Hospital discharge diagnoses are currently recorded using ICD-10-CM codes.

The Danish Cancer Registry contains data on the incidence of cancer in the Danish population since 1943.[16] Reporting to the Cancer Registry has been mandatory since 1987. The diagnosis is coded according to the ICD-10 classification and the ICD-O-3 classification for topography and morphology. Information on treatment and notifying hospital can now be found in linkage with the DNPR and the cause and place of death can be found in linkage with the Danish Register of Causes of Death.

The Danish Registry of Medicinal Product Statistics provides patient-level data and contains data on all prescription drugs dispensed in community pharmacies since 1995.[17] This database collects data on reimbursed and unreimbursed drugs. Dose and duration of prescription use are not available, but can be derived from the number of prescriptions and the dispensed strength. Drugs are coded using the ATC system.

The Danish Register of Causes of Death collects data on causes of death.[18] A death certificate must be filed for every Danish decedent. It is filed by the physician with the most accurate knowledge of the events that led to death. Thus, if the decedent was hospitalized at the time of death, the certificate is filed by a physician working in that hospital department; if the decedent was not hospitalized, it is filed by the decedent's GP. Since 2007, data have been collected electronically.

Earlier versions of this protocol indicated that the Danish General Practice Database (DAMD), which contains patients' clinical data and prescription information related to individual consultations with GPs, who provide all primary care data in Denmark would be included.[19] In 2014, the Danish health authorities have restricted access to this database, so it will no longer be available for this Core study. Loss of this data source has little impact on the quality of the Core studies. The exposure, disease/drug covariates, and the outcomes all have better coverage in the national data resources than in the terminated DAMD database. The only potentially important contribution of the GP database would have been to provide data on lifestyle covariates, such as BMI, smoking and alcohol abuse. Like the other databases, proxies will be used.

9.4.4 Swedish National Databases

In Sweden, all residents are entitled to publicly financed health care covering the entire population, estimated to be 9.6 million in 2013. Many population-based health registries have been established with the use of the unique personal registration number. The personal registration number is given at birth or immigration to all Swedish residents and kept throughout life. In health care, the personal

registration number is used for vital statistics and is also the unique identifier and key variable linking different registers. Information in the registers is recorded by current ICD, ICD-O-3, and/or ATC codes. Data will be obtained from the Total Population Register (with immigrations and emigrations), the NPR (with inpatient and outpatient data), the SCR, the CDR, and the Swedish Prescribed Drug Register.

The NPR includes more than 99% of all somatic (including surgery) and psychiatric hospital discharges.[20] It is mandatory for all physicians, private and publicly funded, to deliver data to the NPR (except for visits in primary care). Previous validation of the NPR by the National Board of Health and Welfare showed that 85%-95% of all diagnoses in the NPR are valid.[21]

The Swedish Prescribed Drug Register (PDR) is a nationwide database covering the entire Swedish population.[22] It includes data that fall into four main categories: (1) patient-specific data, (2) prescriber data, (3) drug data, and (4) pharmacy data. Drug data include the trade name, pharmaceutical form, strength and package size, number of packages, ATC classification code, amount in DDD, and the prescribing and dispensing dates. The information is updated monthly. It does not include the majority of sales of non-prescription over-the-counter medicines, medicines administered at hospitals and nursing homes, or medicines prescribed but not dispensed.

The SCR covers the entire Swedish population. Approximately 50,000 neoplasms are registered every year in Sweden.[23] It is compulsory for every health care provider to report new cases to the registry. The report informs about every cancer diagnosed at clinical, morphological, or other laboratory examinations, as well as cases diagnosed at autopsy. Since 2005, the site and histological type of the cases have been coded in ICD-O-3 codes. A quality study published in 2008 estimated that underreporting was approximately 4%.[24] The Swedish CDR comprises all deaths among Swedish residents, whether occurring in Sweden or abroad.[25] The causes of death are coded according to the international (English) version of ICD-10. The register is updated yearly. In 1994, the nonreporting rate was 0.45% of all deaths.

9.4.5 Humana Database

The Humana Database contains enrollment information linked to medical, laboratory, and pharmacy claims data for the Humana Medicare Advantage and commercially insured members across the US (~14.2 million total current Humana members as of September 2015). The Humana Database covers the time period from 2007 to present. Cancer endpoints can be validated through medical record review. Diagnoses and procedures in the Humana claims database were coded according to the ICD-9-CM system until October 1, 2015 when transition to ICD-10 occurred.

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

the time period from 2007 to the present. As of September 2015, integrated medical and pharmacy data is available for approximately 10.1 million members.

Medicare members remain enrolled with Humana, on average, for 8 years, whereas commercially insured members remain for nearly 2 years. A unique member identifier is assigned to each individual and remains constant regardless of any gap in plan enrollment or transitions between lines of business (Medicare to commercially insured or vice versa).

Member enrollment data contains coverage start and end dates, date of birth, sex, geographic region, death date, race/ethnicity (for Medicare members only), insurance line of business, among others. Medical claims data include information related to facility (inpatient) and provider (outpatient) claims, service date, diagnosis code(s), procedure code(s), place of treatment and associated financial data. Diagnoses and procedures in the Humana claims database were coded according to the ICD-9-CM system until October 1, 2015 when transition to ICD-10 occurred. Pharmacy claims data contain outpatient pharmacy claims (excluding over the counter medication information), prescription fill date, National Drug Code (NDC), quantity dispensed, days' supply, and associated financial data. Laboratory data includes service date, diagnosis code(s), Logical Observation Identifiers Names and Codes (LOINC), lab results and lab vendor. Laboratory data are provided via contractual relationships with major national laboratory service providers. Lab results are not available for all members, nor are laboratory data captured comprehensively for those members with available data.

9.5 Study size

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

CPRD, UK

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

Table 8 Prescriptions for Selected Antimuscarinic and OAB medications, by year (patients aged >=18 and during research quality follow-up in the CPRD primary care data). Clinical Practice Research Datalink, United Kingdom

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

† Up through September 2015

ORD, US

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

Table 9 Initiators of Medications for the Treatment of Overactive Bladder, Optum Research Database (Commercially Insured and Medicare Advantage Members)

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

†Up through June 2015

Danish National Databases

The number of incident and prevalent users of treatments for OAB during April 2013-June 2015 in Denmark is shown in Table 10.

Table 10 Incident and Prevalent Users of Medications for the Treatment of Overactive Bladder, by Year, Danish National Database

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

†Starting April 2013, ††Up through June 2015

Swedish National Databases

The number of incident and prevalent users of medications for the treatment of OAB during 2013-2015 in Sweden is shown in Table 11.

Table 11 Incident and Prevalent Users of Medications for the Treatment of Overactive Bladder, from 2013-2015 in Sweden

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

Humana Database, US

Between 01 January 2013 and 30 June 2015, there were 3,475 unique members with a first (index) dispensing for mirabegron or antimuscarinic medication, who were 18 years or older at the time of first dispensing, had both medical and pharmacy benefits, and had at least 12 months of continuous enrollment prior to the cohort entry date with no claim for the index drug during that 12 month pre-index period. Counts of potential comparator antimuscarinic medications were also assessed using the same criteria. The results are illustrated in Table 12.

Table 12 New Users of Medications for the Treatment of Overactive Bladder: 1 Jan 2013 – 30 Jun 2015 Humana Database

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

† Up through June 2015.

9.6 Data management

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

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

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

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

9.7 Statistical methods

9.7.1 Sample Size Justification

Sample size estimates are based on matching each new user of mirabegron to up to 4 new users of antimuscarinic medications, separately for men and women. Based on current accrual counts from the 5 data sources (through 2015), the analyses of cancer outcomes on cohorts are anticipated to include at least 20,000 person-years of exposure to mirabegron from male subjects (with 80,000 person-years in the comparison cohort, based on 1:4 PS matching) and at least 60,000 person-years with exposure to mirabegron from female subjects (with 240,000 person-years in the comparison cohort). Interim analyses are anticipated to include approximately 50% of the final analysis person-years for all data sources combined, but the proportion contributed from each data source will vary. To account for the conduct of an interim analysis, an adjustment will be made to the estimation of CIs for the primary sex-specific composite outcomes. Specifically, an O'Brien-Fleming adaptation[3] indicates use of a 95.2% CIs for the final analysis of sex-specific composite cancer endpoints. The final analysis should deliver an upper bound of the 95.2% CI of the HR lower than 1.5 with a probability of approximately 90% when the true HR is 1. These estimates are based on an incidence rate of 407.7 per 100,000 person-years for any study endpoint for males and an incidence rate of 303.9 per 100,000 person-years for any study endpoint for females.[4]

9.7.2 Data Analysis

Data will be analyzed separately within each of the 5 databases. For the interim report, the primary analyses will include only those databases linked to cancer registries. These main data sources will include the Danish National Databases, Swedish National Databases as well as the CPRD-DL (linked) database. Unlinked databases will provide supporting evidence. These complementary databases include the CPRD-unlinked (NDL), the ORD, and the Humana databases. For the final report, we propose using all 5 data sources for the primary analyses since the outcomes will be based on validated cases.

Within each data source, 2 cohorts of person-time will be defined following initiation of treatment, including the person-time among new users of mirabegron and the person-time among new users of antimuscarinic medications. The probability of starting treatment with mirabegron relative to antimuscarinic medications, conditional on baseline covariates, will be estimated to create a PS. The cohorts will be PS-matched at a ratio of 1 new user of mirabegron to up to 4 comparator antimuscarinic medication users. For the interim and final reports, all analyses will first be done separately within the Danish National Databases, and Swedish National Databases, the CPRD linked and unlinked databases, the ORD, and Humana databases. Although no individual-level data will be pooled across data sources, meta-analyses of all data sources' estimates will be conducted for the interim and final reports. The meta-analyses will be the primary study analyses for the final report and are the basis for power calculations.

Primary analyses will be an ever-treated analysis, in which once patients are exposed to mirabegron, the remainder of their person-time will be categorized as mirabegron-exposed, even if they switch to an antimuscarinic medication. In contrast, if antimuscarinic medication initiators switch to mirabegron, the remaining person-time will be categorized mirabegron exposed. Unlike a traditional intention-to-treat analysis (ITT) which would tend to reduce the contrast between exposure groups and bias towards a null finding, this method will maintain the contrast between mirabegron and antimuscarinic medications since any event that occurs subsequent to mirabegron exposure will be attributed to mirabegron. Additionally, this methodological choice serves to increase the rigor of the analyses such that no mirabegron-favoring bias can be attributed by an assertion that even patients with brief mirabegron treatment-encounters were excluded from the mirabegron analytical cohort.

9.7.2.1 Interim Report Analysis

The interim analysis will include data summaries from each of the 5 databases. However, primary analyses in the interim report will include only those databases linked to cancer registries. These main data sources will include the CPRD-DL (linked) database, the Danish National Databases, and Swedish National Databases. Unlinked databases will provide supporting evidence. These complementary databases include the CPRD-unlinked (NDL), the ORD, and the Humana databases.

There will be a focus on 4 areas of reporting within each database.

Observed Number of Dispensings/Prescriptions and Length of Follow-up within the Mirabegron Cohort vs the Antimuscarinic Medication Cohort

Prescriptions/dispensings for mirabegron and antimuscarinic medication will be assessed, including an examination of new users that are naïve new users and those new users who switched from other therapies. The interim report will include information on the number and age of new users of mirabegron and antimuscarinic medications, the observed number of dispensings/prescriptions for mirabegron and antimuscarinic medications, and observed length of follow-up. The amount of person-time that will be contributed by mirabegron and comparator antimuscarinic medication users in the cohorts used for the final report will be re-estimated.

Evaluation of Baseline Characteristics of the Treatment Cohorts for PS Matching

A standard set of baseline covariates will be specified based on available covariates (Section 9.3.2). In addition, each data source will identify additional variables for inclusion in the PS based on availability within the data source and an empiric identification process to arrive at a database-specific covariate set for the PS. The empirical approach will determine the 50 most commonly occurring diagnoses, procedures and concomitant medications and their association with mirabegron initiation. A PS will then be estimated using the pre-defined and the empirically-identified covariates. Balance will be assessed using balance diagnostics, including standardized differences. If imbalances remain, covariates may be added to the outcome models. Separate PS will be developed in each calendar year (with partial years included in the adjacent year). The PS and models developed for the interim report time period will remain the same for the final report (i.e., the year-specific PS models for time periods included in the interim report will not be re-estimated for the final report). Each site will provide descriptive statistics and the distribution of the PS for each cohort (mirabegron and antimuscarinic medications). Comparisons of these baseline characteristics across drug-use groupings

will be presented, both prior to and after matching. The matching is done prior to identification of potential cases so is unrelated to the outcomes. The details of the PS estimation and diagnostics will be included in the common SAP.

Estimates of the Cancer Rates and Hazard Ratios (HRs)

The databases may each have different sources for obtaining validated cancer endpoints, some of which require additional linkages to the exposure sources; therefore, sufficient time between the end of patient accrual and preparation of the interim report is needed. As a result, the availability of validated and unvalidated data to summarize endpoints will differ by site. Table 13 summarizes the start and end of the data period to be included in the interim reports. The first date reflects the start of patient accrual. The second date reflects the last date of patient accrual to allow time for full capture of the data (e.g., processing of claims data related to health care utilization and latest available of linked outcomes data).

The estimates of the HRs within each database will be derived according to site-specific PS models and Cox proportional hazards regression models, for the entire population and separately for patients aged 65 years and older. The outcome models will account for the number of matches by conditioning (since some mirabegron initiators will have fewer than 4 matches). The main cancer analysis for the interim reporting of cancer endpoints will include ‘ever exposed’ to mirabegron since cohort entry versus all antimuscarinic OAB drugs, matched by PS. HRs for the male-specific and female-specific composite of the top 10 cancers will be estimated using validated cancer endpoints or algorithms. Results will be stratified into time periods before or after 1 year since index exposure to address potential protopathic bias, which was observed in the validation studies. To address FDA’s concerns about the need for an administrative adjustment to alpha levels due to viewing the interim report estimates of the primary sex-specific outcomes, 99.6% CIs will be included in the interim report alongside 95% CIs for the primary sex-specific outcomes (See Section 9.7.1 for details).

Meta-analysis techniques will be applied to select results in the interim report, providing summaries across the main data sources and additional summaries across the main and complementary data sources. Methods are discussed in Section 9.7.2.4.

Reassessment of Study Power for the Final Study

The number of initiators, estimates of incidence rates of the sex-specific outcomes, and the observed length of follow-up will be used to re-estimate the power for the final report.

Table 13 Data Periods to be Included in the 178-CL-113 Interim Report

Data Source	Data Period	Validation Status For Endpoints
Main Data Sources		
Danish Registers	Mid 2013 – Early 2017	No need for validation
Swedish Registers	Mid 2013 – Dec 2015	No need for validation
CPRD-Linked (UK)	Sept 2012 – June 2014	Cancers identified in GOLD and HES and NCDR
Complementary Data Sources		
CPRD-Unlinked (UK)	September 2012 – Dec 2016	Cancer endpoints will be based on algorithms evaluated in the validation studies.[i]
Optum (US) (ORD)	Late 2012 – Dec 2016	Cancer endpoints will be based on algorithms evaluated in the validation studies.
CHI-Humana (US)	Late 2012 – Dec 2016	Cancer endpoints will be based on algorithms evaluated in the validation studies.

[i] CPRD GOLD is General Practitioner data that meets quality standards, and HES (Hospital Episode Statistics) is hospital data on medical care. NCDR is the National Cancer Data Repository, which consists of tumor level records

9.7.2.2 Analyses for Final Report

All of the analyses described in this section will be completed within each database, after which, the database-specific estimates will be pooled using meta-analytic techniques, as outlined in Section 9.7.2.4.

Within each data source, patients' baseline characteristics will be determined through analysis of data available before the cohort entry date. Baseline characteristics of interest will include demographic variables including age and sex, comorbidities related to OAB, other comorbidities, and specific medication and health care utilization. All baseline covariates will be defined based on all available information, except for the evaluation of health care utilization and concomitant medications which will only be based on the 12 months before cohort entry. Two cohorts will be defined following initiation of OAB treatment: new users of mirabegron and new users of antimuscarinic medications. The distribution of new use of mirabegron and antimuscarinic medications at the time of cohort entry as well as previous use of antimuscarinic medications will be quantified.

Adjustment for potential confounders will be performed by matching on PS to balance cohorts with respect to factors present at or before the time of cohort entry.[26]

Comparison of cancer incidence will be made between mirabegron follow-up time and antimuscarinic medication follow-up time. A range of potential confounders for this comparison of neoplasm endpoints will be addressed through PS matching and the outcomes will be modeled using Cox proportional hazards regression analysis to address differences in follow-up time between the cohorts. Study results will be expressed as estimated adjusted HRs of the endpoints of each study outcome with CIs where the reference will be the antimuscarinic follow-up time. Table 14 provides the sequence of data analyses for the final report.

Preliminary Analysis to Identify Outlier Medications

Each of the database specific validation studies concluded that there was little heterogeneity of cancer risk among the antimuscarinic medications. Nevertheless, to confirm a lack of heterogeneity among the patients included in the PS-matched cohorts, a preliminary analysis will be performed using only the antimuscarinic medication initiators who matched to a mirabegron initiator in the PS-matched cohorts. Age-standardized incidence rates (SIRs) of the sex-specific endpoints will be calculated for each drug and compared to the rates of a combined SIR calculated from initiators of the remaining antimuscarinic medication. [b] For example, the SIR within the oxybutynin initiators will be compared to the SIR calculated for the matched tolterodine, darifenacin, solifenacin, trospium, and fesoterodine initiators, as available in each data source. An antimuscarinic medication will be defined as an outlier if it has a relative risk (RR) > 2.0 and has a SIR with a 95% CI lower limit that exceeds the upper limit of the 95% CI from the comparator group. Similarly, an antimuscarinic will be defined as an outlier having lower risk if it has a RR < 0.5 and the drug that has a SIR with a 95% CI upper limit that is less than the lower limit of the 95% CI from the comparator group.

All subsequent analyses within that data source will exclude matched initiators of that outlier comparator antimuscarinic medication. The corresponding matched mirabegron initiator will be excluded only if that initiator did not match to any other remaining comparator antimuscarinic medication users.

Primary Analyses

The primary analyses will be performed using the sex-specific composite measure, for all patients then restricted to patients aged 65 years and older. In addition, the 10 individual sex-specific cancers will be analyzed, although these analyses will have less precision to assess differences between the exposure cohorts' incidence rates than for the composite cancer endpoints. 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

[b] Patients who initiate 2 antimuscarinic medications on the same day will enter the antimuscarinic medication cohort, but will not be included in this preliminary analysis because they cannot be assigned to a specific antimuscarinic medication cohort.

hysterectomy will not be included in an analysis of uterine cancer alone. A complete list of these exclusions will be outlined in the common SAP.

For all primary analyses, the person-time after antimuscarinic medication initiators switch to mirabegron will be classified as mirabegron-exposed. These Cox models will be used to compare adjusted cancer rates between those patients who were treated with mirabegron and those treated with antimuscarinic medications, stratified by time interval since starting exposure (< 1 year, >=1 year). The proportional hazards assumption will be assessed using log-log plots and inspection of Kaplan-Meier curves.

Increased incidence rates during the first year after starting new use of mirabegron followed by a decrease in incidence during later years could provide evidence of protopathic bias (i.e., treatment for early symptoms of an outcome that appear to cause the outcome) and may also be influenced by surveillance bias in the medical care of new OAB medication users (i.e., increased detection of the endpoint triggered by more intense medical screening when patients start a treatment, rather than resulting from a direct drug effect). Therefore, the study will distinguish between (1) the incidence of cancers that are diagnosed more than 1 year after cohort entry and (2) the incidence of cancers during the first year after cohort entry (to mimic the endpoints observed in clinical trials). The potential for surveillance bias will be addressed by both matching on cancer screening procedures at baseline (by including them in the PS) and by summarizing the occurrence of screening procedures in the follow-up of each cohort as a descriptive characteristic. Each of the validation studies reported substantially higher rates of bladder and prostate cancers within the first 6 months of exposure, suggesting protopathic bias. Therefore, analyses to examine protopathic bias will be conducted to estimate incidence of the composite endpoints and individual cancers in time-since-initiation intervals, e.g., 0 to 6 months, 6 to < 12 months, 12 to < 24 months, >= 24 months.

Secondary Analyses

A series of secondary analyses will be conducted for the final report only.

As noted in the selection criteria, no patients will be included in the cohort if they have prior mirabegron prescriptions or dispensings during all available pre-cohort entry time. However, patients with prior antimuscarinic medication exposure will be allowed to enter the cohort, either as a new antimuscarinic medication user (if a different antimuscarinic medication is initiated) or as a new mirabegron initiator. To evaluate the impact of prior antimuscarinic medication use on the effect of mirabegron on cancer risk, patients will be stratified by new user status. Patients will be classified as naïve new users (no OAB medication prescription or dispensing during the 12 months prior to cohort entry) vs non-naïve new users (a dispensing or prescription for an OAB medication in the 12 months prior to cohort entry).

Another secondary analysis will exclude patients who are immunocompromised, because their cancer risk may be greater than that of the general population. Immunocompromised patients will be identified according to diagnoses listed and drugs prescribed, to be defined in the SAP.

A sensitivity analysis will be conducted in which the person-time contributed by such patients who switch from an antimuscarinic medication to mirabegron will be terminated at the time they switch to mirabegron. The rationale for this analysis is that if switching to mirabegron is common among

patients in the comparator antimuscarinic medication cohort, there could be an imbalance in the length of follow-up time contributed by patients in the 2 cohorts and also because the expected incidence of cancer among such patients would not be entirely independent during the 2 periods of their follow-up.

The risk of cancer in relation to increasing cumulative exposure to mirabegron will also be evaluated. This analysis will be limited to the sex-specific composite measure. As described in the Exposure Section (9.3.1), exposure will be defined. Comparisons of the HRs will be done across tertiles of exposure to mirabegron relative to tertiles of exposure to antimuscarinic medications (e.g., low mirabegron vs low antimuscarinic), as well as to tertiles of exposure among levels of mirabegron exposure (e.g., low mirabegron vs high mirabegron).

Additional details of the statistical analyses will be described in the common Core SAP.

Table 14 Sequence of Modeling for Cancer Outcomes for Final Report

Analysis	Modifications
Preliminary Analyses Outcome: sex-specific composite measures	
HR from Cox, Stratified by < 1, 1+ year since initiation	Site-specific drug-specific analyses to identify outliers in cancer risk. Perform remaining analysis using comparator cohort made of non-outlier drug(s).
Primary Analyses for outcome: sex-specific composite measures	
HR from Cox, Stratified by < 1, 1+ year since initiation	
HR from Cox, Stratified by < 1, 1+ year since initiation	Restricted to age >=65 years old
Sensitivity: HR from Cox	Stratified by 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, >= 24 months since initiation
Primary Outcome Analysis for: 10 individual cancers (sex specific), All patients	
HR from Cox, Stratified by < 1, 1+ year since initiation	
Sensitivity: HR from Cox	Stratified by 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, >= 24 months since initiation

Analysis	Modifications
Secondary Analyses for Outcome: sex-specific composite measures of cancers, All patients	
HR from Cox, Stratified by < 1, 1+ year since initiation	Stratify by naïve vs non-naïve user
HR from Cox, Stratified by < 1, 1+ year since initiation	Exclude immunocompromised patients
HR from Cox, Stratified by < 1, 1+ year since initiation	Censor person-time when an antimuscarinic initiator switches to mirabegron.
HR from Cox, Stratified by < 1, 1+ year since initiation	Stratify by age-group
Cumulative Exposure (compare tertiles of mirabegron to tertiles of antimuscarinic medications), no time stratification	e.g., Compare low mirabegron exposure vs low antimuscarinic medication exposure
Cumulative Exposure (compare within tertiles with mirabegron), no time stratification	e.g., Compare low mirabegron exposure vs high mirabegron exposure

9.7.2.3 Generalizability analysis

Given the difference in patient characteristics and potential confounders across data sources, generalizability of study findings will be assessed. In general, generalizability for cancer studies usually pertains to difference in cancer risk by sex, age and smoking behaviors. The outcomes are sex-specific, so the comparisons will be conducted separately by sex. Since each data source has an internal comparison group (mirabegron relative to antimuscarinic medications), generalizability of study results is based on the relative cancer risk (HR) across data sources. For each data source, HRs will be reported by age-specific stratum (18 to <= 44 years, 45 to <=54 years, 55 to <=64 years, 65 to <=74 years, 75 years and older) to evaluate effect modification by age. Since the quality and completeness of smoking information varies by data source, full examination of HRs by smoking status is not likely to be useful. However, each site will provide information on the prevalence of smoking (or a proxy) and so variations across sites can be assessed.

9.7.2.4 Meta-analysis for Interim and Final Report

The database-specific studies will be conducted according to a common protocol adapted to local database-specific conditions to facilitate future comparison and potential integration of results.[27, 28] No individual-level data will be pooled across data sources, and an appropriate method to combine effect

estimates across data sources will be applied, depending on features of the estimates, including the homogeneity of the estimates across populations.

To address concerns about the generalizability of the estimates from the 5 data sources, database-specific age-standardized HRs for the 2 sex-specific composite endpoints will be reviewed separately. Age categories will be: 18 to <=44 years, 45 to <=54 years, 55 to <=64 years, 65 to <=74 years, 75 years and older. Within each of these age categories, the female and male composite cancer HRs comparing mirabegron to antimuscarinic medications will be tabulated. To address FDAs concerns about the need for an administrative adjustment to alpha levels after viewing the interim report findings, 95.2% CIs will be reported (See Section 9.7.1 for details). For general reporting purposes, standard 95% CIs will also be calculated. If heterogeneity of mirabegron effect is observed (greater than two-fold difference in HR with non-overlapping CIs within a stratum), the meta-analyses will be done by age-specific stratum.

For the final report, all of the primary, secondary and sensitivity analyses outlined in Table 14 will be performed as meta-analyses. For the interim report, meta-analysis of the sex-specific and the 10 sex-specific individual cancers will be done, all stratified by time since initiation (< 1 year, >= 1 year). As these findings are considered preliminary, age-stratum specific HRs will not be reviewed to be considered for exclusion.

Recognizing the internal strengths and limitations of each data source, a meta-analytic approach is appropriate, given anticipated heterogeneity in patient characteristics, prescribing patterns, and availability of covariate information. Standard software for combining estimates across data sources, such as RevMan[29] or Comprehensive Meta-Analysis[30], will be utilized. These software packages perform the meta- analyses and generate diagnostics for assessing heterogeneity along with producing tabular output along with graphical output (forest plot for display of results).

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

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

9.8 Quality control

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

Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP).[31]

9.8.1 Non-Interventional Study Monitoring

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

9.8.2 Direct Access to Source Documents

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

9.9 Limitations of the research methods

The proposed program has several major strengths. One strength is the large, multinational source populations that will provide a strong population base to investigate the risk of neoplasms in association with drugs for OAB in a variety of real-world clinical practice settings. Furthermore, the presence of the endpoints will be identified via direct linkage to registries in the Danish, Swedish, and CPRD-linked data sources, or may be confirmed via medical record review in a subset of the cases in the study populations in the CPRD-unlinked, ORD, and Humana Databases. Finally, this cohort can be the base of future additional endpoint or risk minimization or effectiveness evaluations, if needed.

One limitation is that the analyses will be restricted to the 10 most commonly occurring cancers. More rare cancers will not be examined as outcomes. However, the occurrence of any cancer observed during follow-up will result in censoring for future endpoints. Another limitation of the program is the limited long-term follow-up available to evaluate the occurrence of malignancies, especially among patients with data in US insurance claims databases. Duration of history and follow-up can be limited in the insurance claims database due to individuals changing health insurance plans. By contrast, due to the structure of the included European health care systems, which are supported through taxes and run by the government, the turnover in the European databases is typically lower than in US commercial insurance claims databases. In the CPRD, follow-up is also typically longer than in US commercial insurance claims databases, although it is truncated when patients move and enroll with a practice that does not contribute data to the CPRD. The CPRD intends to expand its base of contributing practices in the future (T. Williams, oral communication, February 2012), which would decrease the probability of patients transferring out of the network of CPRD-contributing practices. A limitation that applies to all populations is the constraint imposed by the currently defined study period, given the long latency of some exposures known to cause malignancies (5-10 years).

It could also be that some of the assumed incident cancers might be prevalent/recurrent cancers if the available baseline period before cohort entry is not long enough to find a previous diagnosis of cancer recorded. The probability of identifying incident cancers depends on the data source for case identification (for example, the SCR records incident cases only) and the type of cancer; the probability that the identified cancer is an incident case increases with longer look-back periods.

Another important limitation will be related to the identification of exposure and endpoint events in the data sources. This proposed program is based on analyses of automated medical and prescription claims and medical records, supplemented with medical record validation of study endpoints in the US and the UK. Although claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the data are collected for the purpose of payment and not research. Drug exposure and effects that do not result in billed medical services will not be identifiable. The presence of a claim for a filled prescription or a record of a prescription issued does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over-the-counter or provided as samples by the physician will not be captured. The presence of a diagnosis code on a medical claim does not provide positive presence of disease, as the diagnosis code may be incorrectly coded or included as a rule-out criterion rather than representing actual disease. This is true also of GP-based databases such as the CPRD.

In the US, the population in the ORD is representative of the privately insured in the US; however, estimates obtained from these analyses may not be generalizable to the uninsured or publicly insured population. The Humana Database contains claims information from Medicare Advantage and commercially insured populations across the US, with higher representation in certain geographic areas where Humana has a larger presence, which may also limit the generalization of the results.

Although methods for confounding adjustment will be implemented, residual confounding is always a concern. We will reduce it by extracting information on all relevant characteristics available on study patients and employing appropriate statistical methodology. During hospitalizations and nursing home stays, data on completeness of exposure, confounders, and possible endpoints may be affected. Additional methods will be explored to evaluate the possibility of residual confounding and its potential effects on the study results.

9.10 Other aspects

Not applicable

10 PROTECTION OF HUMAN SUBJECTS

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

10.1.1 RTI Health Solutions

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

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

10.1.2 Optum

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

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

10.1.3 University of Southern Denmark

The conduct of research entails collaboration with a local university or investigator affiliated with a research institute to access the data. Approvals are required from the Danish Data Protection Agency and the National Health Board. According to Danish law, approval from an ethics committee is not required for a database study.[32] All applications have to be submitted in Danish.

10.1.4 Karolinska Institute, Centre for Pharmacoepidemiology

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

10.1.5 Comprehensive Health Insights

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

10.2 Ethical conduct of the study

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

10.3 Patient information and consent

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

10.4 Patient confidentiality

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

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

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

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

10.5 Insurance of patients

Not applicable

10.6 Other good research practice

The study will be conducted in accordance with the ISPE Guidelines for GPP,[31] the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology[33] and guidelines for study conduct and reporting put forth in the FDA's draft guidance document Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.[34]

The ENCePP Checklist for Study Protocols[35] has been completed (see Annex 2), and the study will be registered in the ENCePP study registry.[36]

The study will comply with the definition of the non-interventional (observational) study provided in the European Union pharmacovigilance legislation adopted 19 June 2012,[37] and the related Guideline on Good Pharmacovigilance Practices (GVP) module VIII on Post-Authorisation Safety Studies[38].

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the new Guideline on GVP, Module VI and VIII:

> *"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."*[39]
>
> *These are retrospective cohort studies involving electronic health care records, and it may not be feasible to make a causality assessment at the individual case level*[38]

Reporting of adverse events will be performed in accordance with the ISPE Guidelines for GPP.[31]

11.1 Definitions of adverse events

Not applicable

11.2 Criteria for causal relationship to the (Study) Drug

Not Applicable

11.3 Procedure in case of pregnancy

Not Applicable

11.4 Notification of adverse drug reactions (serious and non-serious) by Investigator to Sponsor

Not Applicable

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For the interim and final reports, separate study reports will be prepared by all research groups and a combined report will also be prepared by a lead site. Study reports will be sent to the FDA.

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

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

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14 ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	N/A	27 Jun 2016	List of stand-alone documents
2	N/A	27 Jun 2016	ENCePP checklist
3	N/A	27 Jun 2016	Substantial Amendment 3

Annex 2 ENCePP checklist for study protocols

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[c]	☒	☐	☐	26
1.1.2 End of data collection[d]	☒	☐	☐	26
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	26
1.1.5 Registration in the EU PAS register	☐	☒	☐	TBD
1.1.6 Final report of study results	☒	☐	☐	26

Comments:

In Section 10.6, Other Good Research Practice, it is specified that the study will be registered in the ENCePP study registry

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	27
2.1.2 The objectives of the study?	☒	☐	☐	29

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

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	30
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☒	☐	☐	29
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g., cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	30
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	30
3.3 Does the protocol describe the measure(s) of effect? (e.g., relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	57-62

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	30,41
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	24
4.2.2 Age and sex?	☒	☐	☐	41

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.3 Country of origin?	☒	☐	☐	38
4.2.4 Disease/indication?	☒	☐	☐	38
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	41

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g., operational details for defining and categorising exposure)	☒	☐	☐	42
5.2 Does the protocol discuss the validity of exposure measurement? (e.g., precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	42
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☒	☐	☐	42
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	42
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	42

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	30
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	30

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g., collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	43
7.2 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	43

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.1 Exposure? (E.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.).	☒	☐	☐	46-50
8.1.2 Endpoints? (E.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.).	☒	☐	☐	46-50
8.1.3 Covariates?	☒	☐	☐	46-50
8.2 Does the protocol describe the information available from the data source(s) on:				46-50
8.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	46-50
8.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	46-50
8.2.3 Covariates? (E.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.).	☒	☐	☐	46-50
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g., International Classification of Diseases (ICD)-10)	☒	☐	☐	30
8.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	30
8.3.3 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	43
8.4 Is the linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	46-50

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	50,55

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	55-63
10.2 Is the choice of statistical techniques described?	☒	☐	☐	55-63
10.3 Are descriptive analyses included?	☒	☐	☐	55-63
10.4 Are stratified analyses included?	☒	☐	☐	55-63
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	55-63
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	55-63

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	54
11.2 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	64
11.3 Are methods of quality assurance described?	☒	☐	☐	64

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	64
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	64

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	64
12.1.2 Information biases? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	64
12.2 Does the protocol discuss study feasibility? (e.g., sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	55
12.3 Does the protocol address other limitations?	☒	☐	☐	66

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	66

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	68

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	74

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	69
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	69

- Name of the main author of the protocol: Collaborative effort by Research Partners listed on Page3
- Date: 27Jun2016 John D Seeger, on behalf of Research Partners
- Signature: 

Annex 3 Substantial Amendment 3 (27 June 2016)

I. The purpose of this amendment is:

Substantial Changes
1. Interim report – Timing and data sources
DESCRIPTION OF CHANGE:
The timing and the purpose of the interim report have changed.
RATIONALE:
The timing and the purpose of the interim report have changed. Rather than providing a report of patient accrual numbers in June of 2018, an expanded report, including PS-matched HR for the sex-specific composite measures, will be provided in October of 2017. Type 1 error adjustments will be implemented.
2. Interim report –Data sources
DESCRIPTION OF CHANGE:
Databases for the Interim report have been restricted to linked sources.
RATIONALE:
For the interim report, designated Danish, Swedish and CPRD-linked as main data sources, with ORD, Humana and CPRD-unlinked as complementary. This change was implemented after recommendations made during the 21March2016 FDA Type C meeting.
3. Final Report – Full adjudication
DESCRIPTION OF CHANGE: For the final report, rather than rely on algorithms for outcome identification in the ORD, Humana and CPRD-unlinked, adjudication/validation will be completed, when permissions allow.
RATIONALE:
Implemented after recommendations made during the 21March2016 FDA Type C meeting.
4. Meta-analysis methods
DESCRIPTION OF CHANGE: Methods for the meta-analysis have been revised and now conform with standard software to pool estimates across published studies.

RATIONALE:
Research Partners discussed methodology and available software for performing meta-analysis and concluded this approach is preferred because it is standardized, generalizable and replicable.
5. Descriptions of the CPRD-linked and CPRD-unlinked data
DESCRIPTION OF CHANGE: Separate descriptions of the CPRD-linked and CPRD-unlinked data have been provided.
RATIONALE: Implemented after recommendations made during the 21March2016 FDA Type C meeting.

SIGNATURES

APPROVAL PAGE, RTI Health Solutions

Project Title: Post-authorization Safety Study - Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder

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

RTI Health Solutions

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

APPROVAL PAGE, Optum

Project Title: Post-authorization Safety Study - Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder

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

Optum

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

APPROVAL PAGE, University of Southern Denmark

Project Title: Post-authorization Safety Study - Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder

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

University of Southern Denmark

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

APPROVAL PAGE, Centre for Pharmacoepidemiology

Project Title: Post-authorization Safety Study - Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder

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

Centre for Pharmacoepidemiology (CPE)

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

APPROVAL PAGE, Comprehensive Health Insights (CHI)

Project Title: Post-authorization Safety Study - Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder

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

CHI

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

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

Project Title: Post-authorization Safety Program - Evaluation of Neoplasm Events in Users of Treatments for Overactive Bladder

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

Astellas

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