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A Study of Treatments for Overactive Bladder: Incidence and Validation of Cardiovascular and Cancer Outcomes and Examination of Drug-Use Patterns in a US Health Care Claims Data Environment

(Protocol number: 178-CL-115)

Study Report

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APPROVAL PAGE (1 of 1)

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

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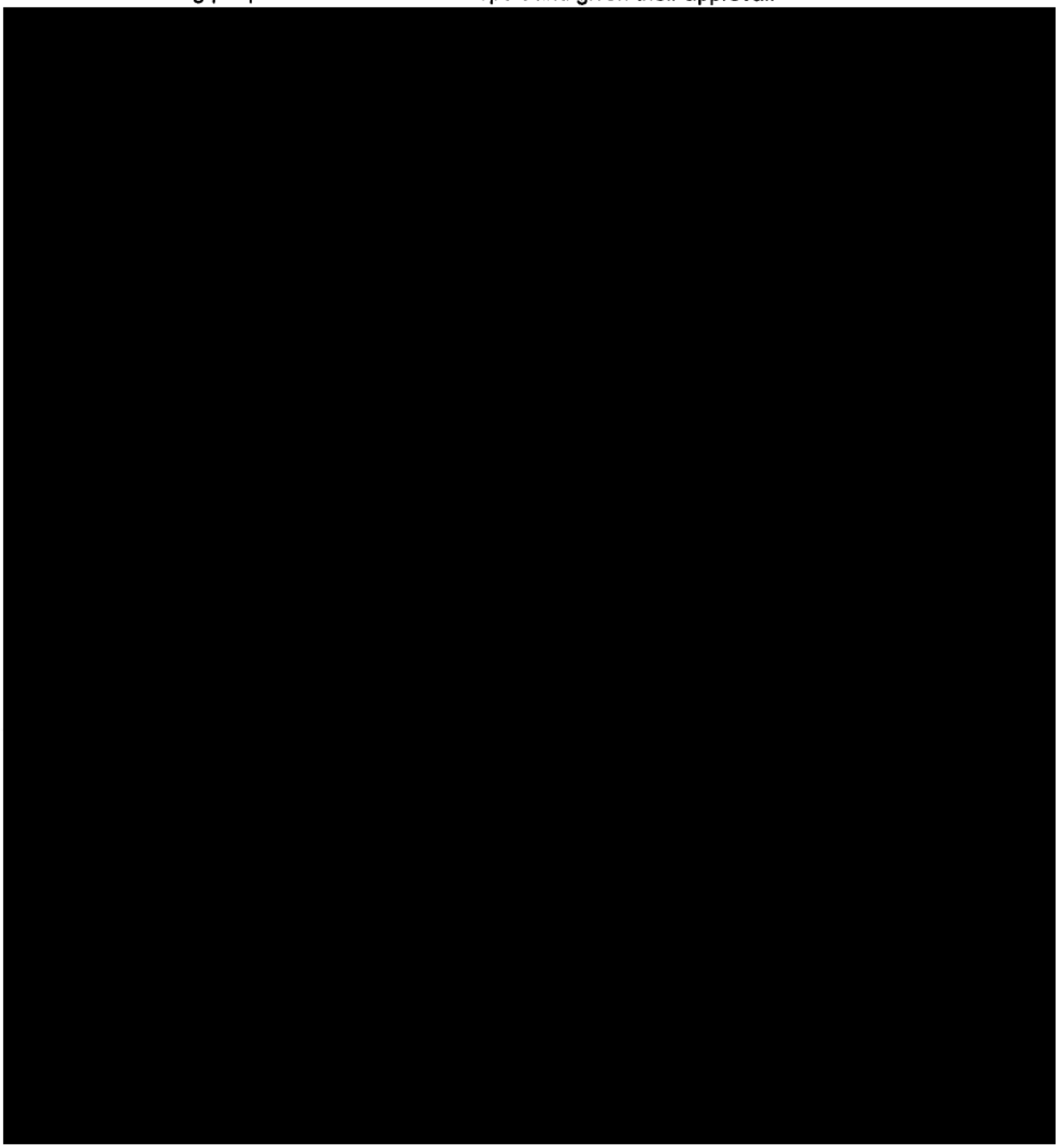

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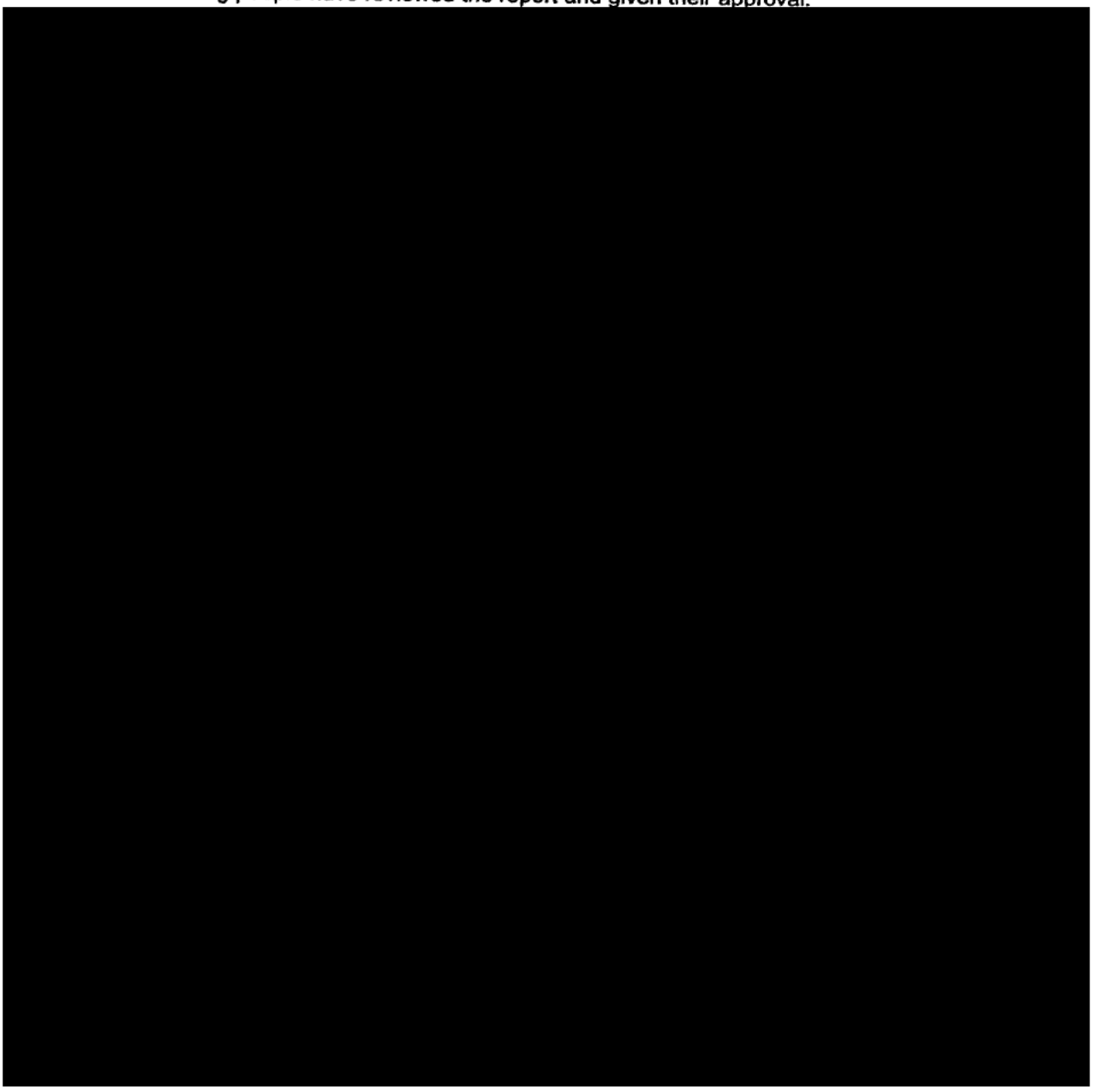

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ABBREVIATIONS

AMI	Acute Myocardial Infarction
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
CV	Cardiovascular
DRG	Diagnosis Related Group
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-9-CM	International Classification of Diseases, Ninth Edition
IR	Incidence Rate
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
MACE	Major Adverse Cardiac Events
NPV	Negative Predictive Value
OAB	Overactive Bladder
ORD	Optum Research Database
PHI	Protected Health Information
PPV	Positive Predictive Value
pys	person-years
SAP	Statistical Analysis Plan
SEER	Surveillance Epidemiology and End Results
US	United States

1. Executive Summary

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. During clinical development, mirabegron at the dose of 50 mg once daily was associated with an increase in pulse rate of approximately one beat per minute compared with placebo and an increase in blood pressure of 0.4 to 0.6 millimeter of mercury (mm Hg) (systolic and diastolic) compared with placebo in patients with OAB.

In a 52-week double-blind randomized trial (Study 178-CL-049), there was a non-significant increase 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, a 12-week phase 2/3 randomized double-blind study (Study 178-CL-047), found a non-significant increase in the risk of benign, malignant, or unspecified neoplasms (including cysts and polyps) among mirabegron 50 mg (3 of 442; 0.7%) and mirabegron 100 mg (2 of 433; 0.5%) groups compared to the placebo group (1 of 453; 0.2%). This numerical imbalance was not observed in 5 other phase 2/3 studies of the same 12-week duration.

These cardiovascular (CV) and cancer effects were considered potential risks by the Food and Drug Administration (FDA) that merited further follow-up. A post-authorization safety program (or post-marketing commitment in the US) has been designed to address these concerns. In preparation for the post-marketing safety assessment of CV and cancer risk associated with mirabegron use, this validation study has been designed to describe drug-use patterns among antimuscarinic drug users, to calculate background incidence rates (IRs) of CV and cancer outcomes among antimuscarinic drug users, to compare incidence rates of CV and cancer outcomes observed during exposed person-time vs. unexposed person-time, and to validate case and covariate-identification algorithms based on the claims data. To address concerns about limiting comparisons to unexposed person-time, an additional exploratory analysis was added to provide a comparison of incidence rates of CV outcomes observed during person-time exposed to each individual drug vs. person-time exposed to any other antimuscarinic medication. The algorithms arising from this work can be implemented in future cohort studies that will include mirabegron users and will improve the efficient and timely evaluation of cancer and cardiovascular safety associated with mirabegron in studies conducted in the US and the European Union (EU), as described in Protocols 178-CL-113 and 114, respectively.

The study findings have been summarized in 2 reports. The majority of the results of claims-based analyses were included in the Interim Report (16 Aug 2013) and, for the readers' convenience, are repeated (with some modifications for clarity and with revised algorithms) in this report. Additional findings based on medical chart abstracted data and additional claims-based analyses are presented for the first time in this Study Report.

Objectives: To develop background knowledge for post-marketing safety evaluations of mirabegron, a study with the following objectives was conducted within the Optum Research Database, a large US electronic healthcare database, capable of linkage to medical records:

1. To characterize users of antimuscarinic medications currently on the US market for the treatment of OAB
2. To describe drug use patterns, including discontinuation, drug switching between antimuscarinic OAB drugs and use of add-on therapies in the first 5 years after FDA approval, among established medications*
3. To estimate IRs of CV outcomes among initiators of antimuscarinic OAB medications
4. To estimate IRs of selected cancer outcomes among initiators of antimuscarinic OAB medications
5. To confirm claims-identified CV outcomes and selected cancer outcomes through medical record review in a sample of patients with potential outcomes of interest and to calculate the associated positive predictive values (PPVs)
6. To provide information for the refinement of the study size and statistical power assessment for post-marketing safety studies of mirabegron
7. To describe the availability of potential confounders in the ORD
8. To calculate the negative predictive value (NPV) of the claims-based algorithms' ability to identify patients as non-cancer cases for each of the 10 types of cancer included in the study. This was done through medical record review in a select sample of patients with at least one claim with a cancer diagnosis, but who did not meet the cancer-case definition.
9. To evaluate the performance of claims-based algorithms for the characterization of up to 5 key cancer-related covariates through medical record review.

The Interim Report included claims-based analyses to address many of the objectives above. This Study Report includes modified claims-based analyses based on preliminary findings as well as results of medical record review. Findings in this Study Report supersede reported preliminary findings presented in the Interim Report.

Data Source: Patients were drawn from a research database containing eligibility, pharmacy, and medical claims data from a large US health plan affiliated with Optum. The Optum Research Database (ORD, formerly known as the Life Sciences Research Database) contains claims and enrollment data dating back to 1993, capturing a longitudinal record of medical services, irrespective of treatment site.

* Use of tolterodine and oxybutynin prior to 2004 will not be included in these analyses.

IRB: This observational study was designed as an analysis of the insurance claims data from a large population with health insurance. Although there was no active enrollment or active follow-up of patients, and no data were directly collected from patients, there are aspects of this analysis that require use of patient identifiers for which approvals are necessary. Approval from the New England Institutional Review Board, including their Privacy Board, was obtained for the study protocol.

Study Populations: The study is focused on users of antimuscarinic medications for the treatment of OAB. Patients in the study were required to meet the following criteria:

- Have a first dispensing for a particular antimuscarinic drug (oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine) during the study period of 01 January 2004 through 30 September 2012
- Age 18 years and older at the time of first dispensing of the antimuscarinic drug during the study period
- Have at least 6 months of continuous enrollment in the health plan (thereby providing medical and drug dispensing history data) before the first dispensing of the antimuscarinic drug

Outcomes: The cardiovascular outcomes of interest include acute myocardial infarction (AMI), stroke, CV mortality (comprised of coronary heart disease death and cerebrovascular disease death), any Major Adverse Cardiac Event (MACE), and all-cause mortality. The cancer outcomes of interest, assessed separately for males and females, include the following types:

Males: bladder, colon/rectum, kidney and renal pelvis, lung and bronchus, melanoma, non-Hodgkin's lymphoma, pancreas, prostate

Females: bladder, breast, colon/rectum, kidney and renal pelvis, lung and bronchus, melanoma, non-Hodgkin's lymphoma, pancreas, uterus

Data Analysis: The analyses included in the Interim Report and repeated or revised in this report include:

- Characterization of antimuscarinic OAB drug users according to baseline covariates, including the addition of an analysis of health plan enrollment length
- Estimation of the IRs and incidence rate ratios (IRRs) of CV outcomes of interest among drug initiators, based on current exposure, using revised algorithms
- Estimation of the IRs and IRRs of cancer outcomes of interest among drug initiators, including the addition of cancer incidence rates by time-since-drug initiation and an evaluation of 6-month and 12-month baseline exclusion criteria
- Evaluation of drug use patterns (e.g., discontinuation and switching between antimuscarinic drugs) within the study period and stratified by time-since approval

The new analyses in this report include:

- Calculation of IRs and IRRs of cancer outcomes based on assignment of “ever or never exposed” to each individual OAB antimuscarinic medication
- Exploratory analysis to compare the IRs and IRRs of CV outcomes observed during person-time exposed to each individual drug vs. person-time exposed to any other antimuscarinic medication
- Calculation of the PPV of claims-identified CV outcomes and selected cancer outcomes through comparison to medical record adjudication results in a sample of identifiable patients with potential outcomes of interest. Comparisons from a determination of case status by the Principal Epidemiology Consultant’s claims profile review also are included.
- Calculation of PPVs for 4 key cancer-related covariates through a comparison to medical record adjudication results
- Calculation of the NPVs of the claims-based algorithms’ ability to identify patients as non-cancer cases for each of the 10 types of cancer through comparison to medical record adjudication results in a select sample of patients with at least one claim containing a cancer diagnosis, but who did not meet the criteria for case status.
- Calculation of observed exposure intervals and incidence rates of key outcomes to allow for the refinement the study size and statistical power assessment for the post-marketing safety studies of mirabegron
- Examination of the overlap of claims-identified outcomes and the distribution of the associated person-time

Results: A total of 205,423 initiators of antimuscarinic drugs were identified during the study period. Patients were classified according to index drug use, including oxybutynin (32%), tolterodine (33%), solifenacin (21%), darifenacin (9%), trospium (3%), and fesoterodine (2%). Nearly half (49%) of the population was less than 55 years old, while 21% were 65 years or older. Women comprised 73% of the population. Only a minority of patients had a diagnosis code in the database suggesting an indication for treatment: 8% of patients having a medical claim with a diagnosis of OAB and 22% of patients having a medical claim for incontinence during the baseline period. Baseline medication use was consistent with the age of the population, with 51% of patients having a dispensing of a CV drug, and 5% of patients having a dispensing of a cancer-related drug. Overall, 48% of patients were defined as being at high risk for CV events.

Application of claims-based algorithms for CV events and mortality resulted in the following IRs (all expressed per 1,000 person-years (pys)): AMI (3.47), stroke (3.33), cardiovascular mortality (0.69), coronary disease death (0.60), cerebrovascular death (0.13), all-cause mortality (3.98), and any MACE event (6.96). For each CV outcome, the IRs were higher among men, older patients, patients with baseline CV conditions, and diabetes. The age, sex-adjusted IRRs of currently exposed person-time to any drug vs. unexposed person-time were: AMI (0.95, 95% CI: 0.86,1.06), stroke (1.15, 95% CI: 1.03, 1.28), cardiovascular mortality (0.97, 95% CI: 0.77,1.24),

coronary disease death (0.89, 95% CI: 0.68,1.15), cerebrovascular death (1.87, 95% CI: 1.12,3.12), any MACE event (1.03, 95% CI: 0.96, 1.12) and all-cause mortality (0.95, 95% CI: 0.85,0.95). When the IRs for exposure to individual medications were compared to IRs within person-time exposed to any other medication (i.e. excluding unexposed person-time), the IRRs were nearly always lower than the IRRs obtained through a comparison to unexposed person-time.

Crude IRs of each of the 10 cancer types were summarized within strata of covariates of interest. For all non-sex specific cancers, men had higher rates than women and patients with diabetes had higher rates than those without. Incidence generally increased with age but stopped increasing or actually decreased after age 75 years. There was a wide range of elevated gender-specific incidence rates during current exposure to any antimuscarinic medication on claims-identified cancer outcomes. After adjusting for age, however, all of the sex-specific cancer incidences (comparing exposure to medications vs. unexposed person-time) were consistent with one another (within chance variation). Comparison of current exposure to individual antimuscarinics, relative to unexposed person-time suggested an elevated incidence of colon/rectal cancer only among men currently exposed to tolterodine (IRR 1.74, 95% CI: 1.01, 2.98). This same finding was observed among men who were ever exposed to tolterodine (IRR 1.82, 95% CI: 1.26, 2.65). In addition, patients who were ever exposed to oxybutynin had an increased incidence of the combined measure of any of the top 10 cancers for both men (IRR 1.27, (95% CI: 1.17, 1.38)) and women (IRR 1.11, (95% CI: 1.01, 1.21)).

Analysis of prescribing patterns of newly-approved drugs (darifenacin, solifenacin, trospium, or fesoterodine) relative to more established drugs (oxybutynin, tolterodine) suggested that the populations were quite similar across groups, except that the index users of the newer drugs were more likely to have a diagnosis of OAB or incontinence. Over the entire study period, 82.2% of patients had dispensings for only one antimuscarinic medication, while 14.4% switched to a single other antimuscarinic drug, and 3.4% receive 3 or more antimuscarinics. For all index drug groups, the most common switch was to oxybutynin. For the oxybutynin index group, the most common switch was to tolterodine.

Preliminary analysis of published cardiovascular algorithms resulted in low PPVs for CV outcomes. Revised algorithms based on input from additional review of claims profiles resulted in a PPV of 100% for AMI and 66% for stroke. High PPVs were observed for most of the 10 cancers outcomes (range of 81% for lung cancer to 100% for breast cancer and 90% for a composite measure of all 10 cancers, among patients without a baseline history of cancer), but low NPVs were observed for the same 10 cancer outcomes (range of 11% to 59%).This may be due to the fact that the exclusion criteria for the cancer analysis were based on a stringent definition of baseline cancer within a subset of patients with at least one claim containing a cancer diagnosis, but who did not meet the criteria for case status. PPVs were calculated for key potential cancer covariates and while the PPV for the evaluation of the presence of diabetes at baseline was high (100%), the algorithm used to define polycystic ovary syndrome at baseline had a much lower PPV (57%).

Abstraction of a subset of patients' medical charts demonstrated that data were incompletely available for several patient characteristics. Examples of the percent of patients with chart information available for specific variables among the cardiovascular charts include: BMI (11%),

weight (66%), height (49%) and smoking status (86%). Chart abstraction provided information on alcohol abuse or treatment on only 3% of patients. Patients for whom cancer charts were obtained tended to be slightly younger than patients eligible for chart abstraction (only 9% vs. 21% of patients were at least age 65 years) but other baseline characteristics were similar.

Conclusion: Two-thirds of the index dispensings were for tolterodine or oxybutynin. The median number of dispensings per person was 2, resulting in an average of approximately 60 days of exposure. The claims-identified baseline characteristics of patients across index drug cohorts were similar. The claims-identified incidence rates of CV and cancer outcomes were lower than external comparisons. Based on claims-identified cases, there was an elevated risk of stroke and cerebrovascular death among the person-time currently exposed to any antimuscarinic medication as compared to unexposed person-time. The age-sex adjusted analyses of claims-identified cancer outcomes did not suggest an elevated incidence rate due to current exposure to antimuscarinic medications as a group. The observed health services utilization and incidence of outcomes was substantially higher among patients over 65 years old relative to younger patients, illustrating an expected age-related increase in healthcare services among commercially insured patients over age 65, suggesting such services are well captured in this database. Updating of published algorithms based on ICD-9 coding changes was essential for accurate identification of potential cases of CV outcomes. The revised algorithm for AMI had a PPV of 100%, while the stroke PPV was 66%. A stringent case definition for cancer outcomes resulted in high PPVs but low NPVs among patients with some evidence of cancer. The patients for whom charts were successfully obtained appear to be representative of the patients with the outcomes of interest. Incidence rates were compared across individual drugs, combinations of drugs, and for unexposed person-time for an array of sex-specific and composite outcome metrics. Therefore, individual estimates reported from this study should be interpreted with consideration of the vast number of comparisons included in these exploratory analyses. The information obtained from this validation study may be used to inform power calculations for the mirabegron Core studies and will help to define the *apriori* hypotheses to be tested.

2. Introduction

On June 28, 2012, [1] Astellas obtained marketing authorization in the US for mirabegron to treat OAB. Approval in the European Union (EU) was obtained on December 20, 2012.[2] The FDA[3] and European Medicines Agency (EMA) each included a post-marketing (US)/post-approval (EMA) requirement to evaluate cardiovascular safety. The FDA also required a post-marketing commitment to evaluate cancer risks.[4] A post-authorization safety program was designed to address these concerns and will be implemented when sufficient patient accrual has occurred. To prepare for a post-marketing safety assessment of CV and cancer risk associated with mirabegron use, this validation study was designed to describe drug-use patterns among antimuscarinic drug users, to calculate background rates of CV and cancer outcomes among antimuscarinic drug users, and to validate outcome-specific claims-based case-identification algorithms. These algorithms, which have been validated using medical chart data, can be

implemented within the Core study that includes mirabegron users to allow for a more efficient and timely evaluation of cancer and cardiovascular risk associated with mirabegron.

3. Study Objectives

To develop background knowledge for post-marketing safety evaluation of mirabegron, Optum conducted a study within a large US electronic healthcare database. The objectives of the study were:

1. To characterize users of antimuscarinic medications currently on the US market for the treatment of OAB
2. To describe drug use patterns, including discontinuation, drug switching between antimuscarinic OAB drugs and use of add-on therapies in the first 5 years after FDA approval, among established medications[†]
3. To estimate incidence rates of CV outcomes among initiators of antimuscarinic OAB medications
4. To estimate incidence rates of selected cancer outcomes among initiators of antimuscarinic OAB medications
5. To confirm claims-identified CV outcomes and selected cancer outcomes through medical records review in a sample of patients with potential outcomes of interest and to calculate the associated positive predictive values (PPVs)
6. To provide information for the refinement of the study size and statistical power assessment for the post-marketing safety studies of mirabegron
7. To describe the availability of potential confounders in the ORD
8. To calculate the negative predictive value (NPV) of the claims-based algorithms' ability to identify patients as non-cancer cases. For each of the 10 cancers of interest, this was done through medical record review in a select sample of patients with at least one claim with a cancer diagnosis, but who did not meet the cancer-case definition.
9. To evaluate the performance of claims-based algorithms for the characterization of up to five key cancer-related covariates through medical record review.

This study incorporated both claims data and medical chart abstraction and adjudication data to achieve the full set of objectives.

[†] Use of tolterodine and oxybutynin prior to 2004 will not be included in these analyses.

4. Methods

4.1 Study Design

Optum conducted a retrospective cohort study within a US-based electronic research database with healthcare information, to estimate the incidence rates of CV and cancer outcomes among initiators of currently available antimuscarinic drugs from 01 January 2004 through 30 September 2012. New users of antimuscarinic drugs were identified, and their demographic characteristics and medication use patterns were described.

4.2 Data Source

The study population is derived from the Optum Research Database (ORD), formerly the Life Sciences Research Database, that contains the eligibility data, medical claims, and pharmacy claims from a large, commercial health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US and comprise approximately 3 to 4% of the US population. The database contains health insurance claims and enrollment data dating back to 1993. For 2012, data relating to approximately 12.6 million individuals with both medical and pharmacy benefit coverage were available. The plan provides fully-insured coverage, minus applicable co-pays, for physician, hospital, and prescription drug services. The providers of these services submit their claims for payment directly to the health plan. Optum uses de-identified data derived from these claims on a daily basis for a wide range of safety, utilization, and economic analyses. The data undergo regular audits and quality control procedures by the insurer and are updated monthly.[‡]

The accessible information includes demographics, pharmacy use, and medical and facility claims, which provide data on services, procedures, and their accompanying diagnoses. The coding of medical claims conforms to insurance industry standards including:

- Use of designated claims forms (e.g., physicians use the Centers for Medicare and Medicaid Services (CMS)-1500 format and hospitals use the UB-92/UB-04 format)
- International Classification of Diseases, Ninth Edition (ICD-9) diagnosis codes and procedure codes
- Current Procedural Terminology (CPT-4) codes
- Healthcare Common Procedure Coding System (HCPCS) codes

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled; pharmacy claims data allowing for longitudinal tracking of medication refill patterns and changes in medications include:

[‡] United Health Group: Data Storage and Tape Management Overview, March 2012.

- National Drug Code (NDC)
- Drug name
- Dosage form
- Drug strength
- Fill date
- Days of supply
- Cost information
- De-identified patient and prescriber codes

4.3 Study Population

Subjects in the study were required to meet the following criteria:

- Have a first dispensing for an antimuscarinic drug (oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine) during the study period of 01 January 2004 through 30 September 2012
- Have reached age 18 years and older at the time of first dispensing of the antimuscarinic drug during the study period
- Have at least 6 months of continuous enrollment in the health plan (thereby providing medical and drug dispensing history data) before the first dispensing of the antimuscarinic drug

Patients with a claim indicative of a cancer diagnosis during the baseline period were excluded from calculation of incident cancer.

A new user of the drugs of interest was defined as a patient who received a first dispensing for an antimuscarinic drug during the study period without a dispensing for the same medication in the previous 6 months. The 6-month period prior to the cohort entry date is considered the baseline period and therefore included 01 July 2003 to 30 September 2012. Only one dispensing of an antimuscarinic drug was required for cohort entry. The study is focused on the evaluation of medical outcomes and prescribing patterns among users of antimuscarinic medications, and not the use of these drugs among a population of patients with a diagnosis of OAB. Consequently, no requirement was made for baseline medical conditions, such as a medical claim indicative of an OAB diagnosis.

4.4 Cohorts

Initiators of each of the 6 antimuscarinic medications were identified. Drug-initiator cohorts were created based on index medication use. A subgroup of patients was defined as being at high risk for cardiovascular events based on having one or more of the following conditions identified by claims in the baseline period: cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmia, hypertension, hyperlipidemia, and diabetes.

4.5 Covariates

All members of the study cohort were classified according to an array of baseline covariates. Covariates were obtained from the 6 months of claims data prior to cohort entry. For the cardiovascular medications, 3 categories were created: antihypertensives, cholesterol lowering, and antiarrhythmic. A composite variable, “any CV drug” also was created. To classify the cancer treatments, 10 categories were created: alkylating agents, antimetabolites, antimicrotubule agents, topoisomerase-active agents, antineoplastic antibiotic, endocrine agents, biologically-directed therapies, immune therapies, miscellaneous anti-cancer agents. A composite variable, “any cancer drug” also was created. A composite variable “any diabetic medication” was created for inclusion in the definition of diabetes.

Although claims data typically provide incomplete capture of information regarding smoking, obesity, and alcohol/substance abuse, a claims-based analysis of these characteristics were completed to allow for the assessment of the availability of data within this cohort.

Additional baseline covariates were defined based on the 25 most frequently occurring diagnoses (at the 3-digit ICD-9 diagnosis level) and procedures (based on CPT, HCPCS, and ICD-9 procedure codes) and medications, through the use of Optum-standardized programs. These were not defined a priori; rather they were identified empirically based on actual occurrence within the data.

Covariates such as family history and occupational exposures are commonly accepted risk factors for CV outcomes. They are however, unlikely to be reliably reported in the medical chart data and are not likely to be related to drug selection, and thus are not considered potential confounders in this study.

For a subset of claims-identified cases, additional covariates such as smoking, treatment for alcohol abuse, height, weight, medical history of diabetes, hypercholesterolemia, hypertension, angina, coronary angioplasty/bypass surgery, arrhythmia, and congestive heart failure were collected from the medical charts detailing the outcome event. This information did not rely on claims codes, rather was abstracted from notes in the medical record.

Four covariates were selected for validation by medical chart abstraction: polycystic ovary syndrome, irritable bowel syndrome, endometrial polyps, and diabetes. These covariates were considered possibly important confounders in the analysis of cancer outcomes and they may be incompletely captured by health insurance claims diagnoses. The claims-based frequencies of these covariates are included in this report.

4.6 Follow-up

For each study outcome, follow-up of eligible subjects started on the day following the first dispensing of an antimuscarinic drug (cohort entry date or index date), and finished at the earliest of:

- End of the study period (30 September 2012)
- Disenrollment from the database

- Occurrence of that particular outcome of interest
- Death
- Dispensing of two antimuscarinic medications on the same day

Patients were allowed to have more than one of the study outcomes (e.g. AMI followed by cancer), so each of these events has been identified independently, with the associated person-time for each outcome captured separately. However, patients who met the algorithm criteria for any of the 10 cancers no longer accrued either events or person-time for future cancer events of a different type.

4.7 Exposure

After standard data reconciliation programs were run on the dispensing data, each day of person-time was classified into mutually exclusive categories of exposed person-time and unexposed person-time based on specific drug use. For exposed person-time for each individual medication, the "quantity of drug dispensed" was used to characterize exposure. This data field is likely more reliable than "days' supply" since it is the basis for payment and therefore undergoes extensive review before the data are finalized.[5] Based on observed dispensing dates and quantities within our data, dispensing quantity was assumed to correspond to person-days of exposure. The only exception was oxybutynin tablets (5 mg, standard release), for which it was assumed that quantity divided by 2 corresponded to person-days of exposure since this drug was typically used twice per day. Given that patients were unlikely to take the medication exactly as prescribed (e.g. complete a 30-day supply in exactly 30 days), a grace period of 7 days of exposure was added to each dispensing. This value was empirically derived based on the inter-dispensing intervals observed. Each day of follow-up (and the corresponding grace period) was classified based on current exposure to one drug only. Follow-up time where there were no antimuscarinic drugs dispensed was considered unexposed person-time. Because exposure to an antimuscarinic medication was required for cohort entry, all patients contribute some exposed person-time, and unexposed person-time is contributed following at least some exposure to OAB medication.

An additional assessment of exposure was defined for an analysis of cancer outcomes, based on "ever exposed to each individual drug vs. never exposed to each individual drug". Each person-day was classified as never exposed to oxybutynin (for example), until a first dispensing of oxybutynin. Subsequent days of follow-up were classified as ever exposed to oxybutynin and any events that occur during that follow-up time were classified as occurring during person-time exposed to oxybutynin. Events prior to the initial dispensing of oxybutynin were classified as occurring during never exposed to oxybutynin person-time. If this same patient switched to tolterodine, the patient had some days that were classified both as ever exposed to oxybutynin and ever exposed to tolterodine, and those same days were classified as never exposed to each of the other OABs of interest. Because the cohort consists only of patients who initiate antimuscarinic medication treatment, it was not possible to do an analysis of ever exposed vs. never exposed to *any* of the antimuscarinic medications, i.e. all unexposed person-time follows some antimuscarinic exposure.

Special attention was devoted to the evaluation of switching between antimuscarinic drugs within specific timeframes. For person-time calculations, it was assumed that use of a particular drug was terminated upon the dispensing of another drug and all subsequent person-time was assigned to the new drug until either the days' supply (plus grace period) was exceeded, the new dispensing was observed, or follow-up period ended. Because of the complexity and tenuous assumptions involved in developing person-time estimates from dispensing data for use of syrups, patches, or gels, patients with dispensings for these formulations were excluded from analyses that are based on person-time.

4.8 Outcomes

Within the claims database, each of the following individual outcomes of interest was evaluated based on algorithms including diagnoses reported on inpatient and outpatient claims.

4.8.1 Cardiovascular

The components of Major Adverse Cardiac Events (MACE) were examined separately and as a composite measure.

- Acute myocardial infarction (AMI)
- Stroke
- CV mortality§
    - Coronary heart disease death
    - Cerebrovascular death
- Any MACE event (AMI, stroke or CV death)
- All-cause mortality

During the initial proposal and protocol development period, it was determined that death would be assessed on the claims-level only (as defined in Section 4.8.1.3) during the validation study. In contrast, the design and timeline for Protocols 178-CL-113 and 178-CL-114 includes validation of death through a National Death Index (NDI) search.

The validation was done in done in several steps:

- Case identification using originally- proposed algorithms;
- Medical chart review, case adjudication, and calculation of PPVs for each endpoint;
- Re-assessment of the algorithm through additional claims profile review;
- Definition of adjusted algorithm;

§ Death was assessed at the claims code level only.

- Assessment of concordance between the adjusted algorithm and the adjudicated cases.

4.8.1.1 AMI

In the Interim Report, the algorithm for AMI was defined by having at least one claim with an ICD-9 diagnosis code 410 in the first or second position of the hospital or emergency room admission diagnosis.[6,7,8,9,10] Preliminary analyses which compared claims-based case identification with medical chart adjudicated case identification suggested that additional refinements to the AMI algorithms were necessary due to a lower than expected PPV.

Two additional AMI algorithms were evaluated. Given the exploratory nature of these algorithms, case classifications were expanded from “case”, “questionable”, and “non-case” to “probable”, “possible” or “non-cases”. The first AMI algorithm (referred to as Algorithm A) was defined based on diagnostic codes only (ICD-9 and Diagnosis Related Groups (DRG) codes). Because some AMIs are averted by the intervention of revascularization procedures, a second algorithm (Algorithm B), which includes revascularization procedure-related codes, also was included in order to capture these events. Both algorithms considered the occurrence of death.

AMI Algorithm A:

Probable cases included patients with:

1. 2+ claims with AMI ICD-9 codes

or

2. 1 claim with an AMI code along with claims for death[**]

or

3. A claim with a DRG consistent with AMI

Possible cases included patients with:

1. One claim with an AMI ICD-9 code

and

2. No claims for death

and

3. No claims with a DRG consistent with AMI

[**] The algorithm for identifying deaths is described below. Only deaths within 30 days of claims with an AMI code was included in deaths for the AMI algorithm.

Non-cases included patients without claims with AMI ICD-9 diagnosis codes or DRG codes.

AMI Algorithm B:

Probable cases included patients with:

1. 2+ claims with AMI ICD-9 codes

or

2. 1 claim with an AMI code along with claims for death or revascularization,

or

3. A claim with a DRG consistent with AMI or revascularization

Possible cases included patients with:

1. One claim with an AMI ICD-9 code and no claims for death or revascularization

and

2. No claims with a DRG consistent with AMI or revascularization

Non-cases included patients with no claims with AMI ICD-9 diagnosis codes and no claims with a DRG consistent with AMI or revascularization.

The diagnosis, revascularization and DRG codes, and the relevant time intervals are outlined in Appendix 1.

4.8.1.2 Stroke

In the Interim Report and early versions of the protocol, stroke was defined based on the presence of hospital diagnosis codes 430, 431, 433.x1, 434.x1 and 436, located in the first position only.[11,12] Preliminary analyses suggested that additional refinement to the stroke algorithm was necessary, due to changes in ICD-9 coding and a low PPV. A revised algorithm is presented below. Given the exploratory nature of these algorithms, case classifications were expanded from “case,” “questionable”, and “non-case” to “probable”, “possible” or “non-cases”.

Patients with any of the following baseline characteristics were excluded prior to the implementation of the stroke algorithm:

- History of stroke, defined as the presence of a claims with an ICD-9 diagnosis code for ischemic or hemorrhagic stroke
- The presence of at least one code indicating a cancer diagnosis
- At least one dispensing for warfarin
- A code for atrial fibrillation

The algorithm considered diagnosis, procedure, and DRG codes related to ischemic and hemorrhagic strokes. Also considered were claims for medical imaging and medical, physical and occupational therapies or equipment after the potential stroke is identified.

The algorithm for stroke was defined in the following way:

Probable cases were defined by the presence of claims that meet both criteria 1 and 2. Patients with criterion 3 also were considered probable cases:

1. At least one claim with a ischemic stroke ICD-9 diagnosis code or at least one hemorrhagic stroke ICD-9 code (without head injury)

and

2. At least one claim with a code indicative of medical imaging, post-stroke physical or occupational therapies or equipment, anticoagulant medical therapy(for ischemic strokes only) or death[††]

or

3. A claim with a DRG for stroke

Possible cases were defined by:

1. The *presence* of at least one claim with an ischemic ICD-9 code or at least one hemorrhagic ICD-9 code (without head injury)

and

2. The *absence* of claims with codes indicative of scans, post-stroke physical or occupational therapy or equipment, anticoagulant medical therapy (for ischemic strokes only), or death

Non-cases were defined by criteria 1 and 2. Patients who met criterion 3 also were considered non-cases:

1. The *absence* of any claims with ischemic or hemorrhagic stroke ICD-9 codes

and

2. The *absence* of a claims with a DRG for stroke

or

3. The *presence* of a claim with a hemorrhagic stroke code and a qualifying head injury code

---

[††] The algorithm for identifying deaths is described in section 4.8.1.4. Only deaths within 30 days of claims with a hemorrhagic or ischemic code were included in deaths for the stroke algorithms.

The diagnosis, procedure, and DRG codes and the relevant time intervals for the stroke outcome and exclusion criteria are outlined in Appendix 1.

4.8.1.3 CV Mortality

CV mortality was defined based on the presence of an indicator for death (as defined in section 4.8.1.4) and at least one of code for coronary heart disease or cerebrovascular disease within 7 days prior or 30 days after the date of death. The codes for each type of death are outlined in Appendix 1. Two types of death were combined into the CV mortality definition (coronary heart disease (CHD) death and cerebrovascular death). A patient may be classified as both a CHD death and a cerebrovascular death if codes for each type of outcome appear near the time of death, but a patient only contributes once to the total of CV mortality.

Deaths associated with accidents (defined by the presence of a claim with an ICD-9 code beginning with E (external causes of injury) in the 7 days prior or 30 days after the date of death), or malignancy (defined by the presence of a claim with a malignancy code in the 7 days prior or 30 days after the date of death), were not counted as CV deaths, even if the definition for CV death was otherwise met during this interval.

4.8.1.4 All-cause Mortality

Patient death was defined by the presence of either criterion 1 or 2 and criterion 3 was required for the patient death definition:

1. One or more inpatient or ER claim with patient status listed with the following discharge status codes:

    20 = expired

    40 = expired at home

    41 = expired in medical facility

    42 = expired – place unknown

or

2. At least one claim with ICD-9 diagnosis code 798.XX (sudden death) or 427.5 (cardiac arrest)

and

3. no claims more than 30 days after criterion 1 or 2 [‡‡]

[‡‡] Note: There was a 30-day grace period allowed for claims to accrue after the date of patient status=expired or ICD-9=798,427.5)

4.8.1.5 MACE Composite Endpoint

The composite outcome major adverse cardiac events (MACE)—acute myocardial infarction, stroke, or CV mortality—was added to later versions of the protocol. A binary indicator of "any MACE event, yes/no" was created. The person-time for this outcome stopped accruing on the date of the first observed CV event.

4.8.2 Cancer

The observed neoplasms in the mirabegron clinical development program were those that occur commonly in the general population, therefore the list of cancer outcomes included each of the 10 most commonly occurring malignancies in the US based on those with the highest age-adjusted incidence rates between both genders in the US SEER data, 2005-2009.[13] Gender-specific outcomes were created.

Table A: Diagnosis Codes for the Claims-based Algorithms for the Identification of Cancer Outcomes

Cancer Type	ICD-9 codes	Cancer Type	ICD-9 codes
Bladder	188.xx	Melanoma	172.xx
Breast (females only)	174.xx	Non-Hodgkin's Lymphoma	200.xx 202.xx
Colon/Rectum	153.xx 154.xx	Pancreas	157.0x-157.3x, 157.8x, 157.9x
Kidney and renal pelvis	189.0x 189.1x	Prostate (men only)	185.xx
Lung and bronchus	162.xx	Uterus (females only)	182.xx

The presence of a single claim in isolation, or multiple claims confined to a short period of time (e.g. < 30 days) is likely to represent a rule-out diagnostic process rather than reflect a diagnosed cancer case. To create an algorithm that would separate likely cases of cancer from unlikely ones, a literature search was undertaken along with consultation with a practicing oncologist who has extensive experience with medical claims data. An algorithm for each cancer was developed using the codes listed in Table A. In general, to be categorized as a potential case, a person was required to have 2 or more claims 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.

In addition, for each type of cancer, an indicator was created to identify the occurrence of 2 or more claims that were at least 30 but not more than 90 days apart during the baseline period. Patients identified as having any one of the 10 cancers during baseline were not included in the at-risk population for any of the 10 incident cancers (e.g. a history of breast cancer disqualified a person from subsequent time at risk for incident uterine cancer). The presence of any claims with an ICD-9 code for history of cancer (ICD-9-CM: V10) during the baseline period also led to the patient being excluded for future cancer events.

4.9 Medical Record Abstraction and Adjudication

Optum is restricted from seeking medical charts for some patients based on employer-health plan administrative contracting requirements that are not related to the individual patient health characteristics. Among the remaining subset of patients, the following multi-step process was undertaken to identify and retrieve medical records for abstraction. (See Figure 1).

4.9.1 Profile Review (Round 1)

For each outcome and covariate of interest, a random sample of patients was identified and detailed claims profiles of inpatient, outpatient and pharmacy services near the time of the diagnoses were generated. Optum contracted with a nurse experienced in working with health insurance claims data to perform a review of claims profiles. The profile review step did not include case adjudication; rather the purpose of the profile review was to identify the appropriate claim indicating a medical chart with the greatest likelihood of having sufficient information to validate the diagnosis. For example, inpatient charts typically provide more complete information on the range of patient services than charts obtained from a specialist. The decision to seek a particular chart for a particular patient is made strictly on clinical grounds (i.e. which chart is likely to have the most information needed to correctly diagnose the patient). The profile reviewer identified an alternate location should the first selection be unavailable. Efficiency across patients by selecting sites of service from which multiple medical records could be obtained never entered the decision. There are no gains in efficiency from preferentially choosing that site over a more clinically relevant one since the medical records are sent securely from each site to the abstractors and no on-site visit is required. The charts retrieved will not, and should not be representative of the ORD as a whole, but they will be representative of members of the study cohort who have an outcome of interest. The profile reviewer then selected the location (facility or provider) where the chart is located. Using Optum developed software for profile reviews, the profile reviewer chose the claims line that corresponds to the medical record of interest and that information was used to contact the selected provider and to request access to the chart.

4.9.2 Obtaining and Abstracting Medical Records

Optum contracted with an outside vendor to procure the medical records and perform the medical record abstraction. The abstraction firm has expertise in coordinating with providers and abstracting information from medical charts. Abstractions were conducted by trained health information management abstractors. The list of items in the abstraction checklist was developed by Optum. The abstractors obtained a copy of the patient medical records covering the relevant period of care and abstracted the medical documents specified by the abstraction checklist. For cancer profiles, documents from the period +/- 180 days around the case-identifying claim date were included. For cardiovascular and covariate profiles, documents from the periods +/- 90 days around the case-identifying claim date were included. These windows were defined through clinical input as the most likely to identify medical records that would permit confirmation of the diagnosis. Although the abstraction vendor has in place and follows its own standard operating procedures (SOPs) for process and quality control, Optum held the contracted abstraction firm accountable to achieve an acceptable abstraction rate and quality standards, such as a minimum number of attempts at contacting the facility or provider. The obtained charts were de-identified and blinded with respect to protected health information (PHI)/personally identifying information (PII). Blinding of the drug was not required in the validation study because there was not one drug of interest relative to other drugs.[§§]

4.9.3 Adjudication

Optum established two physician panels (one for CV outcomes and one for cancer outcomes). Each panel consisted of three clinical consultants with expertise in the specific clinical area to perform the outcome adjudication. Initially, each chart and the corresponding abstracted information were reviewed by two members who classified case status as case, questionable, non-case, or insufficient information. The results of the case status and the estimated date of onset (for confirmed cases) were entered into an electronic data capture tool by the adjudicator. These data were incorporated into the study analytic SAS dataset.

Where necessary, Optum worked with all panel members to arrive at consensus adjudications. If no consensus was reached, the third panel member's adjudication was accepted to settle any discordant classifications.

Adjudication of non-cases (for cancer NPV) and covariates where less clinical expertise and judgment is required did not involve a committee. A single clinical consultant reviewed the clinical data from each medical record for the randomly selected potential non-cases and evaluated the presence of covariates.

Some post-marketing safety studies require medical record review of every claims-identified case to rule out false positives. Given that this was a validation study designed to demonstrate

§§ Blinding will be required in the safety study to evaluate mirabegron relative to other OAB medications.

the methods of using administrative claims database rather than a study of the safety of currently available medications, a random sample of charts for each outcome was reviewed.

For the CV endpoints, the decision regarding the number of charts to be obtained was based on the complexity of the outcome and the corresponding billing codes. For stroke, 123 charts were sought due to the complexities of defining stroke (e.g., claims for ischemic versus hemorrhagic stroke, with the exclusion of transient ischemic accident events). Identification of possible acute myocardial infarction events is less complex and therefore a smaller number of charts (n = 35) were sought.

For each of the 10 selected cancers, charts for 40 patients with claims-algorithm identified cancer during follow-up were sought (n=400) for the calculation of cancer-specific PPVs. In addition, for the same 10 selected cancers, charts for approximately 30 patients who were *not* classified as cancer cases but whom had at least one claim with a cancer diagnosis code in the follow-up period were sought (total n=298) for the calculation of the NPV. This cancer-specific approach was necessary because the predictive value of each algorithm is influenced by the prevalence of the disease. For example, the number of true breast cancer cases is substantially higher than the number of true pancreatic cancer cases. Therefore, the likelihood that a claims-based algorithm fails to correctly identify cases is a function of the size of the underlying population of true cases. The calculation of cancer-specific NPVs provides more valuable information regarding each algorithm's performance than would a validation process that combined all cancers into one analysis.

For 4 cancer-related covariates (diabetes, polycystic ovary syndrome, irritable bowel syndrome, and endometrial polyps), charts for approximately 40 patients were sought (total n=156) for the calculation of each positive predictive value. These covariates are potential cancer risk factors that are readily identified in claims data and were selected by a clinician familiar with multivariable analysis of cancer outcomes in claims data.

4.9.4 Claims Profile Review to Refine Stroke and AMI Algorithms (Round 2)

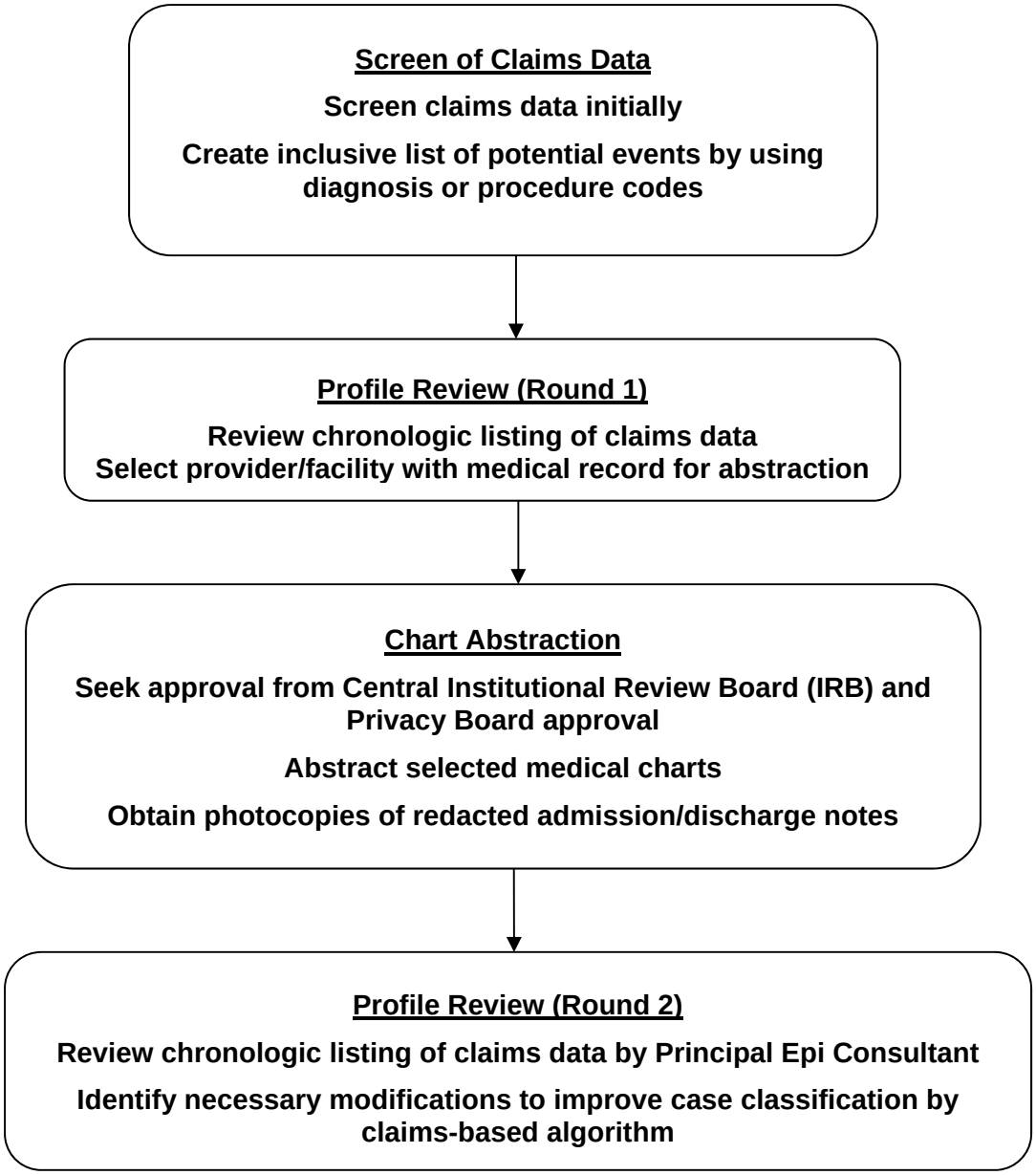
Because this study was exploratory rather than confirmatory, an additional round of profile review was added to the study after review of the results of the preliminary analysis of the proposed AMI and stroke algorithms. A round of clinical expert profile review was added to provide input on potential revisions to the claims-based algorithm. The goal was to identify major elements (such as revascularization or physical therapy) that would be indicative of the outcome (AMI and stroke, respectively) rather than limit the revisions to a very specific set of codes that appeared among the subset of patients. The addition of these major elements may contribute to an algorithm that is more predictive of future performance and not study specific. Among patients for whom Optum had a chart which has already been adjudicated in the preliminary analysis within this validation study, the Principal Epidemiology Consultant (PEC) on the study reviewed the claims profiles to identify additional services indicative of AMI or stroke.

Additional exclusion criteria (such as evidence of cancer, history of stroke or atrial fibrillation) were identified through this process. The information obtained through this review was used to inform the details of the algorithms presented in sections 4.8.1.1 and 4.8.1.2. These algorithms

were applied to the data and the case status was compared to the case status assigned by the PEC. Discrepancies were noted and profiles were re-reviewed for further refinement. An additional PPV was calculated to summarize the comparison between the claims-based case status and the PEC-based case status.

Having the profiles reviewed by the PEC provided information about the value of an additional review of profiles to improve case identification. For the main safety study, the latter approach may represent an intermediate level of outcome ascertainment that has greater PPV than the computer algorithm, but may have a lower PPV than full chart adjudication.

Figure 1. Chart Abstraction and Event Verification Process



5. Data Analysis Methods

The goal of the study was to demonstrate what pertinent information could be reliably obtained from the administrative database and the medical records and to describe medication use patterns, as a basis for post-marketing studies of mirabegron use. As such, this validation study did not include hypotheses to be tested to compare one drug relative to a comparator group or include the complex statistical analysis that is central to the future main mirabegron safety study. Rather, all analyses were descriptive in nature both for the health insurance claims data and the medical record review data. Analyses were conducted in SAS version 9.2.

5.1 Claims-based Characterization of Antimuscarinic Medication Users

Demographics, plan membership characteristics, diagnosis of OAB or incontinence and other comorbidities, along with prescription drug history, and health care services were summarized for the entire cohort and separately for users of each antimuscarinic. The drug used at cohort entry was used to classify each patient. The categorical characteristics are shown in Table A1, which includes the count and corresponding percentage. The continuous characteristics are shown in Table A2, which includes the median and interquartile range (IQR). Tables A1.1 and A2.1 present the same baseline characteristics stratified by age group (< 65 years old, ≥ 65 years and older), rather than stratified by index drug group. Tables A3.1 – A3.3 include the counts and corresponding percentage for each of the top 25 diagnoses, procedures, and medications identified during the baseline period. Length of enrollment in the health plan was summarized from start of enrollment until index drug use, index drug use through end of enrollment, and start to end of enrollment (Table A4). Median enrollment lengths are presented for the overall cohort, by age and by baseline history and follow-up presence of CV or cancer events. The characteristics of the patients who were prescribed gels, syrups, or patches vs. the remainder of the cohort were presented. The categorical characteristics are shown in Table A5a, which includes the count and corresponding percentage. The continuous characteristics are shown in Table A5b, which includes the median and IQR.

5.2 Incidence of Claims-Identified CV Outcomes

For each of the CV outcomes of interest, claims-based algorithms were used to identify the potential cases, as defined in section 4.8.1. For AMI and stroke, the number of possible cases was extremely small and therefore only probable cases were considered as cases. Counts for possible and non-cases were combined. The primary AMI outcome definition included AMI diagnosis and revascularization codes. The individual CV outcomes were presented to evaluate the homogeneity of the occurrence of each outcome across baseline characteristics and medications. A composite MACE measure also was reported.

The number of cases, the associated person-years, and the crude incidence rates were calculated for the entire cohort, as well as stratified by a variety of demographic characteristics and baseline comorbidities, as identified in Table B1. The incidence rates were calculated by summing the number of claims-identified cases and dividing the sum by the number of person-years of follow-up. Incidence rates were presented as the number of cases per 1,000 pys.

To obtain drug-specific incidence rates, the number of cases that were identified during current exposure (separately for each drug and for unexposed person-time) was divided by the sum of the person-years of current exposure (or non-exposure). For example, the total number of cases of AMI that occur when a patient was currently exposed to oxybutynin was divided by the person-years of current exposure to oxybutynin to obtain the incidence rate. Similar calculations were done for each drug, for all drugs combined, and for unexposed person-time, as summarized in Table B2. Note that the number of patient-years exposed to a treatment varies across outcomes because the intervals of time-at-risk differed.

For each drug and all drugs combined, crude and age group (at baseline) and gender-adjusted IRRs were estimated with Poisson regression, with unexposed person-time as the reference group. Additional IRRs of the IR within person-time with current exposure to a particular drug divided by the IR in current exposure to any other drug (i.e. excluding all non-exposed person-time) also were estimated. For all IRR calculations, Proc Genmod (SAS version 9.2) was used, specifying the Poisson distribution and log of the person-time for an offset term. Estimates were exponentiated to provide crude and adjusted incidence rate ratios. The 95% confidence intervals (CIs) for the crude and adjusted IRRs also are presented (Table B2).

Additional analyses were restricted to the population age 65 years and older (Table B2.1) and individuals with high CV risk as defined in section 4.2 (Table B2.2).

5.3 Incidence of Claims-Identified Cancer Outcomes

For each of the ten cancer outcomes of interest, a claims-based algorithm was used to identify the potential cases, as defined in Section 4.8.2.

The number of claims-identified cancer outcomes by time since index drug use was summarized for each cancer type, separately by gender. Intervals were defined as 0-6 months, 6-12 months, 1-<2 years, 2+ years after index drug use.*** The person-years of follow-up within each interval were calculated. The crude incidence rate was calculated by dividing the number of cases within an interval by the number of person-years of follow-up during that interval. Incidence rates were presented as the number of cases per 1,000 pys. Patients who had cancer during the standard 6-month baseline were excluded, where baseline cancer is defined as described in Section 4.8.2 (Table C1a). A sensitivity analysis was conducted in which patients who have cancer during a 12-month baseline period were excluded (Table C1b).

Stratified analyses of the gender-specific claims-based cancer outcomes were reported for a series of baseline characteristics, as outlined in Table C2.

*** In earlier protocol versions and in the Interim Report, cancers that occurred within the first year after exposure were not included in incidence rates. Based on further discussions between Astellas/Optum/FDA, a decision was made to include all cancers since baseline but to present the information on the rates by time-since-index drug exposure.

Crude and age-group (at baseline) adjusted IRs, IRR and 95% CIs of each of the individual gender-specific cancer outcomes based on current treatment were estimated with Poisson regression for each of the individual medications to evaluate the homogeneity of the ratios across medications. The rate of outcomes identified during currently exposed person-time was compared to the rate of outcomes observed during unexposed person-time. Note that the number of patient-years exposed to a treatment varied across outcomes because the intervals of time-at-risk differed (Table C3).

Analyses also were conducted with exposure defined as “ever exposed vs. never exposed” to each individual drug. Because the cohort consisted only of patients who initiate antimuscarinic medication treatment, it was not possible to do an analysis of “ever exposed vs. never exposed to *any* of the antimuscarinic medications”. Results were summarized in Table C4.

Analyses presented in Tables C1-C4 were repeated, including only patients who were age 65 years or greater at baseline (Tables C1a.1, C1b.1, C2.1, C3.1, C4.1).

5.4 Evaluating Drug Use Patterns

For each patient and each antimuscarinic medication, the total number of dispensings over the study period was summarized (mean, median, IQR).

Antimuscarinic medications were classified based on the time since drug approval: older medications (oxybutynin, tolterodine) vs. more recently approved medications (solifenacin, darifenacin, fesoterodine, trospium). The characteristics of patients whose index drug was an established medication vs. a newly approved medication were compared. Categorical variables were summarized by frequency and percentage (Table D1a). Continuous variables were summarized by mean and standard deviation as well as median and interquartile range (Table D1b).

The study period started several years after oxybutynin and tolterodine were launched. In contrast, for the other antimuscarinic drugs, the study period will include use immediately after approval, which may be the most informative regarding what might be observed among early initiators of mirabegron.

Table B: Approval Date for Antimuscarinic Medications for Treatment of OAB

Drug	Date of approval	Date of First Observed Dispensing in Study Period
Oxybutynin	1975	01 January 2004*
Tolterodine	1996	01 January 2004*
Solifenacin	November 2004	13 January 2005
Darifenacin	December 2004	01 February 2005
Fesoterodine	October 2008	17 March 2009
Trospium	May 2004	27 August 2004
*Due to study protocol start date		

Special attention was devoted to the evaluation of switching between antimuscarinic drugs within specific timeframes and termination of drug regimens. The results will have major

implications on the person-time estimates and statistical power in the main mirabegron safety studies. Among the patients who had dispensings for at least 2 unique antimuscarinics, drug switching and consistency of use over the study period was evaluated. As outlined in Table D2, for each index drug and for each patient, the number of dispensings of the index drug (prior to switching and after switching if use of the index drug was resumed) was summarized. Similarly, the number of dispensings of the drug to which the patient switched was summarized. The interval between the end of the use of the index drug and the date of the dispensing of the second drug also was calculated. The counts of number of patients who switched were provided. The number of dispensings and time intervals were summarized by medians and IQRs.

5.5 Calculation of Positive Predictive Values (PPV) Based on Chart Review

A random sample of claims-identified CV and cancer cases were validated by review of the medical record. In addition, a sample of claims-identified cancer-related covariates was validated. For each outcome (or covariate), the PPV of the claims-based algorithm was calculated based on chart-validated case (or covariate) status. The number of medical records requested, obtained, and confirmed, along with the PPV and 95% CI are presented. The PPV was calculated as the number of confirmed cases (or confirmed covariates) divided by the number of medical records obtained containing sufficient information for case confirmation. This methodology is currently in use in the mini-Sentinel project funded by the FDA.[14] Additional calculations of the sum of the confirmed and questionable cases divided by the total number of charts were included. These data are presented in Tables E1 (PPVs for CV), E2 (PPVs for cancer), and E3 (PPVs for covariates). Calculations based on the Principal Epidemiology Consultant's additional profile review of the obtained CV charts also are reported in Table E1, using the same methodology.

The impact of the PPVs on the IRs of the outcomes is of interest. It is possible to estimate the amount of person-time that was incorrectly removed from the denominator for each of the rejected cases in the validated sample, and then project that amount out to the full population. In most situations, however, the possible correction is small, since it pertains only to missed person-time in the cases that should have been rejected. This error is likely to be much smaller than the error that arises from uncertainty about the true value of the PPV. Similarly, it is possible that multiplying the case count by the PPV is an over-correction. This would come about if the rejected cases were to go on to become true cases shortly later. For example, patients who have had small, non-transmural infarcts, and who as a consequence do not have the right EKG findings or the requisite troponin levels, may nonetheless be a very high risk for a true AMI in the near future. If the first event were abstracted and rejected as an AMI, the second event may not even have been considered. Therefore, formal calculations would tend to obscure the uncertainty involved and were not performed.

5.6 Calculation of Negative Predictive Values (NPV) Based on Chart Review

Preliminary frequencies in the data suggested that the vast majority of patients did not have a single claim with a cancer diagnosis during follow-up (89%). Given that it would be highly unlikely that a patient without *any* claims with a diagnosis code has cancer, the estimation of the NPV for the cancer algorithm was performed within the subset of patients with at least one claim with a diagnosis code for one of the 10 cancer types of interest during follow-up, but excluding patients who met the definition of cancer during the follow-up period.[†††] A random sample of claims-identified potential non-cancer cases were validated by review of the medical record. For each outcome, the NPV of the claims-based algorithm was calculated based on chart-validated case status. The number of medical records requested, obtained, and confirmed, along with the NPV and 95% CI is presented. The NPV was calculated as the number of confirmed non-cases divided by the number of medical records obtained containing sufficient information for case confirmation. An additional calculation of the sum of the non-cases *and* questionable cases divided by the total number of charts were included. These data are presented in Tables F1.

5.7 Information from Medical Charts

Data abstracted from the medical charts of potential CV and cancer cases were summarized in Tables G1a (CV, categorical variables), G1b (CV, continuous variables), G2a (cancer, categorical variables), and G2b (cancer, continuous variables) Data are presented for all charts obtained, as well as by antimuscarinic initiator group. For categorical variables, the number (n) and percentage (%) of cases with each value is presented. Abstractors were given the following categories for smoking: not recorded, never/non-smoker, former smoker, current smoker, or other, and the following categories for weight: underweight, normal weight, obese, not recorded, or other. Among patients for whom values of height, weight or BMI are available, the n, mean, standard deviation, median and IQR is reported. All other covariates were coded as “Yes” or “No/Not recorded”.

A comparison of the patient characteristics among those eligible for cancer chart abstraction and the patients for whom charts were sought and charts were obtained is provided in Tables G3a (continuous characteristics) and G3b (categorical characteristics).

[†††] Very early in the protocol implementation period, it was discussed that using a random sample of patients, the majority of whom would have no evidence of cancer, was unlikely to be a useful exercise to evaluate the cancer algorithm (with a specific number and timing of codes). A decision was made to restrict the chart selection and associated NPV estimation to patients with some evidence of cancer. This decision was included in the Statistical Analysis Plan (SAP) and later versions of the protocol.

5.8 Additional Data Analyses

Some patients experienced multiple outcomes (e.g. AMI followed by cancer several years later). The order of the first 2 events, as well as the distribution of the associated person-time between events is summarized (median, IQR, mean, range) in Table H1. Note that the person-time accrual stopped at the time of the first diagnosis of one of the top 10 cancers, so the overlap analysis was restricted to “any cancer” rather than *each* of the 10 cancer types.

6. Institutional Review Board / Privacy Board Approvals

This observational study was designed as an analysis of the insurance claims data from a large population with health insurance (ORD). The machine-readable dataset of the ORD can be augmented on an ad hoc basis by further inquiry, including chart review. The data are only re-identified following approval by an appropriate institutional review board/privacy board, and all data access conforms to applicable Health Insurance Portability and Accountability Act (HIPAA) policies. There was no active enrollment or active follow-up of patients, and no data were directly collected from patients. Approval from an institutional review board (IRB) and their privacy board was obtained since the study includes information from medical record abstraction for which patient identifiers are necessary. The IRB reviewed and approved the protocol and study materials related to the chart abstraction process such as provider letters and chart-abstraction forms. Optum Epidemiology study investigators analyzed the data.

7. Results

7.1 Characterization of OAB Drug Users

Tables A1 and A2 display the baseline characteristics of the 205,423 initiators of antimuscarinic drugs identified during the study period. Patients were classified according to index drug use including oxybutynin (32%), tolterodine (33%), solifenacin (21%), darifenacin (9%), trospium (3%), and fesoterodine (2%). Nearly half (49%) of the population was younger than 55 years old, while 21% were 65 years or older. 73% of the population were women. While 8% of patients had a medical claim with a diagnosis of OAB during the baseline period, 22% of patients had a medical claim for incontinence. The baseline prevalence of hypertension and hyperlipidemia were similar (both 33%) and a substantially lower percent of patients had baseline cardiovascular disease (7%), angina (0.8%), coronary artery disease (6%), ischemic heart disease (6%) or AMI (0.2%). A similar profile was seen for medication use: a much higher percentage of patients had baseline use of antihypertensives (43%) and cholesterol lowering therapies (28%) than baseline use of antiarrhythmics (19%). Overall, 51% of patients had baseline use of any CV drug, in contrast to 7% with a baseline history of cancer and 5% of patients had a dispensing of a cancer-related drug. The median number of inpatient days during the 6-month baseline was 0 (IQR: 0,0), and among the 28,269 patients with at least one inpatient day, the median number of inpatient days was 3 (IQR: 2,6). The cohort of patients over the age of 65 years had a higher proportion of males (39.3% vs. 23.6%) and more patients with baseline classification of high CV risk (78.6% vs. 40.0%) and longer median enrollment length (36 vs. 27 months).

During the 6-month period prior to index use, some of the most common comorbidities include symptoms involving the urinary system (ICD-9 788, 52%), essential hypertension (ICD-9 401, 36%) and disorders of lipid metabolism (ICD-9 272, 34%) (Table A3.1). Some of the most common CPT-4 codes (excluding office visits (CPT-4 99213, 99214) were collection of venous blood by venipuncture (CPT-4 36415, 40%), lipid panel (CPT-4 80061, 31%), and unlisted diagnostic, radiographic procedures (CPT-4 76499, 28%) (Table A3.2). The most common medications include genitourinary smooth muscle relaxants (100%, representing the index dispensing), opiate agonists (39%) and quinolones (28%) (Table A3.3).

The median length of membership in the insurance plan from start of enrollment to end of follow-up was 58 months and was longer among older people and those with CV or cancer outcomes during follow-up (Table A4).

Patients who were ever prescribed gels, patches, or syrups (n=9,733) were compared to all other users (n=195,690) and were more likely to be women, older age, and have a diagnosis of incontinence (Tables A5a, A5b).

7.2 Incidence of CV Outcomes

The incidence rates of CV outcomes by select baseline characteristics are presented in Table B1. Crude and age-sex adjusted analyses of each of the CV outcomes within exposed and unexposed person-time are presented in Table B2 (stratified by index drug cohorts), B2.1 (restricted to patients age $\geq$ 65 years and older) and B2.2 (restricted to patients with high CV risk at baseline). A summary of the findings for each outcome is presented below.

7.2.1 Incidence of AMI

Based on AMI Algorithm A, there were 1,482 probable cases, 321 possible cases, and 203,620 non-cases. With the addition of DRGs for Algorithm B, the number of probable cases increased to 1,535, while the number of possible cases was 268, with 203,620 non-cases.

Overall, the claims-based IR for AMI, based on a case definition based on Algorithm B (probable cases) was 3.47. The IRs among the exposed (any drug) person-time and unexposed person-time were 3.86 and 3.32, respectively. The age-sex adjusted IRR of AMI among exposed (any drug) vs. unexposed person-time was 0.95 (95% CI: 0.86, 1.06). The range of adjusted IRRs included 0.75 (95% CI: 0.61, 0.92) for solifenacin person-time vs. unexposed person-time to 1.06 (95% CI: 0.89, 1.27) for oxybutynin vs. unexposed person-time. All of the drug-specific AMI IRRs were consistent with the reference group (within chance variation) when the reference group was person-time exposed to any other antimuscarinic medication, except for the association between solifenacin use and risk of AMI compared with exposure to any other OAB drugs (adjusted IRR=0.73, 95%CI: 0.59,0.92).

Overall, the claims-based IR for AMI among patients > 65 years at index date, based on Algorithm B (probable cases) was 8.80. The IRs among the exposed (any drug) person-time and unexposed person-time were 8.49 and 8.96, respectively. The age-sex adjusted IRR of AMI among exposed (any drug) vs. unexposed person-time was 0.95 (95% CI: 0.83, 1.10). The range of adjusted IRRs included 0.76 (95% CI: 0.57, 1.00) for solifenacin person-time vs.

unexposed person-time to 1.06 (95% CI: 0.84, 1.34) and 1.06 (95% CI: 0.53, 2.13) for oxybutynin and fesoterodine vs. unexposed person-time, respectively. All of the drug-specific AMI IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any other antimuscarinic medication.

Overall, the claims-based IR for AMI among patients with high cardiovascular event risk[‡‡‡], based on Algorithm B (probable cases) was 5.84. The IRs among the exposed (any drug) person-time and unexposed person-time were 5.98 and 5.78, respectively. The age-sex adjusted IRR of AMI among exposed (any drug) vs. unexposed person-time was 0.96 (95% CI: 0.85, 1.08). The range of adjusted IRRs included 0.76 (95% CI: 0.61, 0.96) for solifenacin person-time vs. unexposed person-time to 1.07 (95% CI: 0.88, 1.30) and 1.07 (95% CI: 0.59, 1.93) for oxybutynin and fesoterodine vs. unexposed person-time, respectively. All of the drug-specific AMI IRRs were consistent with the reference group (within chance variation) when the reference group was the person-time exposed to any other antimuscarinic medication, however one association between solifenacin use and risk of AMI when compared with exposure to any other OAB drugs is not consistent with a chance difference (adjusted IRR=0.75, 95% CI: 0.56,0.96).

7.2.2 Incidence of Stroke

There were 24,159 patients excluded from the stroke algorithm calculation due to baseline history of stroke, cancer diagnosis, use of warfarin or claims for atrial fibrillation. The stroke algorithm identified 1,474 probable cases of stroke, with only 10 possible cases and 179,780 non-cases.

Overall, the claims-based IR for a stroke case definition based on probable cases was 3.33. The IR among the exposed (any drug) person-time and the unexposed person-time were 4.24 and 2.98, respectively, and the age-sex adjusted IRR was 1.15 (95% CI: 1.03, 1.28). The range of adjusted IRRs included 0.65 (95% CI: 0.31, 1.38) for fesoterodine vs. unexposed up to 1.23 (95% CI: 0.96, 1.58) for darifenacin vs. unexposed person-time. All of drug-specific stroke IRRs were consistent with the reference group (within chance variation) when the reference group was the person-time exposed to any other antimuscarinic medication.

Overall, the claims-based IR for stroke among patients $\geq$ 65 years at index date was 8.33. The IRs among the exposed (any drug) person-time and the unexposed person-time were 9.21 and 7.85, respectively, and the age-sex adjusted IRR was 1.16 (95% CI: 1.01, 1.33). The range of adjusted IRRs included 0.75 (95% CI: 0.31, 1.80) for fesoterodine vs. unexposed up to 1.40 (95% CI: 1.04, 1.89) for darifenacin vs. unexposed person-time. All of drug-specific stroke IRRs

‡‡‡ Patients with a high risk for cardiovascular events were defined as having one or more of the following conditions identified by claims in the baseline period: cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmia (separately for diagnosis and medications), hypertension (separately for diagnosis and medications), hyperlipidemia (separately for diagnosis and medications), diabetes.

were consistent with the reference group (within chance variation) when the reference group was the person-time exposed to any other antimuscarinic medication.

Overall, the claims-based IR for stroke among patients with high cardiovascular event risk was 5.29. The IRs among the exposed (any drug) person-time and the unexposed person-time were 6.03 and 4.94, respectively, and the age-sex adjusted IRR was 1.10 (95% CI: 0.98, 1.25). The range of adjusted IRRs included 0.67 (95% CI: 0.30, 1.50) for fesoterodine vs. unexposed up to 1.22 (95% CI: 0.93, 1.61) for darifenacin vs. unexposed person-time. All of drug-specific stroke IRRs were consistent with the reference group (within chance variation) when the reference group was the person-time exposed to any other antimuscarinic medication.

7.2.3 Incidence of CV Death (combined)

Overall, the claims-based IR for CV death was 0.69. The IRs among the exposed (any drug) person-time and the unexposed person-time were 0.82 and 0.64, respectively, and the age-sex adjusted IRR was 0.97 (95% CI: 0.77, 1.24). The range of adjusted IRRs included 0.54 (95% CI: 0.17, 1.68) for trospium vs. unexposed up to 1.61 (95% CI: 0.60, 4.33) for fesoterodine vs. unexposed person-time. All of the drug-specific CV death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

Overall, the claims-based IR for cardiovascular death among patients $\geq$ 65 years at index date was 2.27. The IRs among the exposed (any drug) person-time and the unexposed person-time were 2.28 and 2.26, respectively, and the age-sex adjusted IRR was 1.01 (95% CI: 0.77, 1.33). The range of adjusted IRRs included 0.44 (95% CI: 0.11, 1.79) for trospium vs. unexposed up to 1.06 (95% CI: 0.67, 1.67) for oxybutynin vs. unexposed person-time. All of drug-specific CV death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

Overall, the claims-based IR for cardiovascular death among patients with high cardiovascular event risk was 1.27. The IRs among the exposed (any drug) person-time and the unexposed person-time were 1.29 and 1.26, respectively, and the age-sex adjusted IRR was 0.92 (95% CI: 0.71, 1.19). The range of adjusted IRRs included 0.38 (95% CI: 0.10, 1.55) for trospium vs. unexposed up to 1.71 (95% CI: 0.63, 4.59) for fesoterodine vs. unexposed person-time. All of drug-specific CV death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

7.2.4 Incidence of Coronary Heart Disease Death

Overall, the claims-based IR for coronary heart disease death was 0.60. The IRs among the exposed (any drug) person-time and the unexposed person-time were 0.67 and 0.57, respectively, and the age-sex adjusted IRR was 0.89 (95% CI: 0.68, 1.15). The range of adjusted IRRs included 0.59 (95% CI: 0.19, 1.85) for trospium vs. unexposed up to 1.34 (95% CI: 0.43, 4.18) for fesoterodine vs. unexposed person-time. All of the drug-specific CHD death

IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

Overall, the claims-based IR for coronary heart disease death among patients ≥ 65 at index date was 2.02. The IRs among the exposed (any drug) person-time and the unexposed person-time were 1.92 and 2.08, respectively, and the age-sex adjusted IRR was 0.92 (95% CI: 0.69, 1.24). The range of adjusted IRRs included 0.48 (95% CI: 0.12, 1.94) for trospium vs. unexposed up to 1.12 (95% CI: 0.59, 2.14) and 1.12 (95% CI: 0.28, 4.54) for darifenacin and fesoterodine vs. unexposed person-time, respectively. All of drug-specific CHD death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

Overall, the claims-based IR for coronary heart disease death among patients with high cardiovascular event risk was 1.13. The IRs among the exposed (any drug) person-time and the unexposed person-time were 1.10 and 1.15, respectively, and the age-sex adjusted IRR was 0.85 (95% CI: 0.65, 1.12). The range of adjusted IRRs included 0.42 (95% CI: 0.10, 1.68) for trospium vs. unexposed up to 1.39 (95% CI: 0.44, 4.34) for fesoterodine vs. unexposed person-time. All of the drug-specific CHD death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

7.2.5 Incidence of Cerebrovascular Death

Overall, the claims-based IR for cerebrovascular disease death was 0.13. The IRs among the exposed (any drug) person-time and unexposed person-time were 0.23, 0.10, respectively, and the age-sex adjusted IRR was 1.87 (95% CI: 1.12, 3.12). The range of adjusted IRRs included 0.00 (95% CI: 0.00, --) for trospium vs. unexposed up to 2.83 (95% CI: 0.39, 20.72) for fesoterodine vs. unexposed person-time. This estimate is based on 1 death during the fesoterodine-exposed person-time. There were 9 deaths each during the solifenacin-exposed person-time (IRR: 2.44, 95% CI: 1.16, 5.12) and tolterodine-exposed person-time (IRR: 1.92, 95% CI (0.91,4.05). All of the drug-specific cerebrovascular death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

Overall, the claims-based IR for cerebrovascular disease death among patients ≥ 65 years at index date was 0.37. The IRs among the exposed (any drug) person-time and unexposed person-time were 0.54 and 0.28, respectively, and the age-sex adjusted IRR was 1.93 (95% CI: 1.01, 3.68). The range of adjusted IRRs included 0.00 (95% CI: 0.00, --) for fesoterodine and trospium vs. unexposed up to 2.48 (95% CI: 0.99, 6.26) for oxybutynin vs. unexposed person-time. All of the drug-specific cerebrovascular death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

Overall, the claims-based IR for cerebrovascular disease death among patients with high cardiovascular event risk was 0.22. The IRs among the exposed (any drug) person-time and the unexposed person-time were 0.32 and 0.18, respectively, and the age-sex adjusted IRR was 1.74 (95% CI: 0.98, 3.08). The range of adjusted IRRs included 0.00 (95% CI: 0.00, --) for

trospium vs. unexposed up to 3.30 (95% CI: 0.45, 24.37) for fesoterodine vs. unexposed person-time. All of the drug-specific cerebrovascular death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

7.2.6 Incidence of All-cause Mortality

Overall, the IR for claims-based all-cause mortality was 3.98. The IRs among the exposed (any drug) person-time and the unexposed person-time were 4.42 and 3.80, respectively, and the age-sex adjusted IRR was 0.95 (95% CI: 0.85, 1.05). The range of adjusted IRRs included 0.79 (95% CI: 0.60, 1.03) for darifenacin vs. unexposed up to 1.10 (95% CI: 0.94, 1.30) for oxybutynin vs. unexposed person-time. The age-sex adjusted IRR for all-cause mortality for person-time exposed to oxybutynin compared to exposure to any other antimuscarinic medication was 1.24 (95% CI: 1.03-1.49).

Overall, the IR for claims-based all-cause mortality among patients $\geq$ 65 years at index date was 10.70. The IRs among the exposed (any drug) person-time and the unexposed person-time were 10.20 and 11.00, respectively, and the age-sex adjusted IRR was 0.94 (95% CI: 0.83, 1.06). The range of adjusted IRRs included 0.75 (95% CI: 0.36, 1.58) for fesoterodine vs. unexposed up to 1.07 (95% CI: 0.87, 1.31) for oxybutynin vs. unexposed person-time. All of the drug-specific all-cause mortality IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication.

Overall, the IR for claims-based all-cause mortality among patients with high cardiovascular event risk was 6.66. The IRs among the exposed (any drug) person-time and the unexposed person-time were 6.71 and 6.64, respectively, and the age-sex adjusted IRR was 0.93 (95% CI: 0.83, 1.04). The range of adjusted IRRs included 0.75 (95% CI: 0.55, 1.01) for darifenacin vs. unexposed up to 1.06 (95% CI: 0.89, 1.27) for oxybutynin vs. unexposed person-time. All of the drug-specific cerebrovascular death IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any antimuscarinic medication, except for the association of solifenacin with all-cause mortality when comparing with exposure to any other OAB drugs (IRR=0.79, 95% CI:0.63, 0.99).

7.2.7 Incidence of Any MACE Event

Overall, the IR for claims-based major adverse cardiac events was 6.96. The IRs among the exposed (any drug) person-time and the unexposed person-time were 8.27 and 6.46, respectively, and the age-sex adjusted IRR was 1.03 (95% CI: 0.96, 1.12). The range of adjusted IRRs included 0.74 (95% CI: 0.46, 1.19) for fesoterodine vs. unexposed up to 1.10 (95% CI: 0.98, 1.24) for tolterodine vs. unexposed person-time. All of the drug-specific any MACE event IRRs were consistent with the reference group (within chance variation) when the reference group was defined as the person-time exposed to any other antimuscarinic medication, except for the association between solifenacin use and any MACE outcome when compared to the rate in person-time exposed to any other OAB drugs (IRR=0.85, 95%CI:0.73,0.99).

Overall, the IR for claims-based major adverse cardiac events among patients ≥ 65 years at index date was 18.00. The IRs among the exposed (any drug) person-time and the unexposed person-time were 18.40 and 17.80, respectively, and the age-sex adjusted IRR was 1.03 (95% CI: 0.94, 1.14). The range of adjusted IRRs included 0.81 (95% CI: 0.46, 1.43) for fesoterodine vs. unexposed up to 1.12 (95% CI: 0.97, 1.29) for tolterodine vs. unexposed person-time. All of the drug-specific any MACE event IRRs were consistent with the reference group (chance variation) when the reference group was defined as the person-time exposed to any other antimuscarinic medication.

Overall, the IR for claims-based major adverse cardiac events among patients with high cardiovascular event risk was 11.50. The IRs among the exposed (any drug) person-time and the unexposed person-time were 12.30 and 11.10, respectively, and the age-sex adjusted IRR was 1.01 (95% CI: 0.93, 1.10). The range of adjusted IRRs included 0.76 (95% CI: 0.46, 1.26) for fesoterodine vs. unexposed up to 1.10 (95% CI: 0.96, 1.26) for oxybutynin vs. unexposed person-time, and the association between solifenacin use and any MACE outcome when compared to the rate in person-time exposed to any other OAB drugs was an IRR of 0.83 (95%CI:0.71, 0.98).

7.3 Incidence of Claims-Identified Cancer Outcomes

7.3.1 Summary of Cancer Findings

A total of 13,746 patients were identified as having a history of cancer during or prior to the 6-month baseline period, 5,143 of which were age 65 years or older. These numbers include patients with a general history of cancer (ICD-9 code V10) and patients who met the algorithm for at least 1 of the select 10 cancers in this report. Separately by cancer type, summary counts of the number of cases identified within various time periods relative to index drug use are presented in Table C1a. These counts provide insight into the timing of incident cancers relative to time-since-drug initiation. The analysis is repeated in Table C1a.1, restricted to patients who were age 65 years and older at index date. In Tables C1b (all ages) and C1b.1 (age 65 years and older), the length of the baseline period was expanded to identify and exclude cancers which were prevalent during a 12-month rather than 6-month baseline. Based on the extended baseline period, 16,432 patients with prevalent cancers were excluded from the all-age analysis and 6,411 were excluded from the age group 65 years and older analysis.

Among men, the total number of incident cancers (all 10 types combined) was 2,408 (IR 25.57) based on a 6-month baseline exclusion and decreased to 2,299 (IR 24.88) based on a 12-month baseline exclusion. For the women, the total number of incident cancers (all 10 types combined) was 2,204 (IR 7.02) based on a 6-month baseline exclusion and decreased to 2,088 (IR 6.73) based on a 12-month baseline exclusion.

The number of cases of each type of cancer, associated person-years and IR are presented, stratified by a series of baseline characteristics for all age groups (Table C2), and for patients age 65 years and older (Table C2.1). For all cancer types, the IR are higher among men than women (except sex-specific cancers) and among diabetics. For most cancers, the rates

increase with age, although for kidney, lung, pancreas, prostate and uterine cancer, rates were slightly higher among ages 65-74 relative to ages 75 years and older.

Crude and age, sex-adjusted IRRs, based on current exposure to each individual antimuscarinic and all drugs combined, are presented in Tables C3 (all age groups) and C3.1 (age 65 years and older). After adjustment for age, there was an elevated risk for colon/rectum cancer among patients currently exposed to tolterodine (IR 1.74 (95% CI: 1.01, 2.98)). For all medications combined, the age-adjusted IRR for all ten cancers identified during currently exposed person-time vs. currently unexposed person-time was 0.84 (95% CI: 0.76, 0.92) for men and 0.81 (95% CI 0.74, 0.89) for women.

Crude and age-sex-adjusted IRRs, based on ever-exposed to each individual antimuscarinic and all drugs combined, are presented in Tables C4 (all age groups) and C4.1 (age 65 years and older). After adjusting for age, the risk of cancer associated with ever-exposed was elevated for oxybutynin (men: IR 1.27 (95% CI: 1.17, 1.38), women: (IR 1.11 (95% CI: 1.01,1.21)), for bladder cancer and oxybutynin (men: IR 2.49 (95% CI: 2.08,2.98), women: (IR 2.35 (95% CI: 1.78,3.10)), for colon/rectum cancer and tolterodine exposure (men: IR 1.82, (95% CI: 1.26, 2.65)), and for kidney cancer and oxybutynin (women: IR 1.72, (95% CI: 1.11,2.66)). When the population was restricted to patients age 65 years or older at baseline, an elevated risk was observed for all cancers among patients ever-exposed to oxybutynin (men: IR 1.16 (95% CI: 1.03, 1.31), women: IR 1.23 (95% CI 1.06, 1.43)), for bladder cancer (men: IR 2.08 (95% CI: 1.58, 2.74)), women: IR 2.12 (95% CI 1.42, 3.18)), for cancer of the lung/bronchus among men exposed to solifenacin (IR 1.60 (95% CI: 1.01, 2.51)), and for cancer of the colon/rectum among men exposed to tolterodine (IR 2.40 (95% CI: 1.40, 4.10)).

7.3.2 Cancer-specific Findings

The incidence of bladder cancer was 1.68 cases per 1,000 pys, but was substantially higher among men (IR 5.10), patients with claims evidence of smoking (IR 6.65), COPD (IR 5.59), or renal impairment (IR 5.33). When restricted to the population age 65 years and older, the IR of bladder cancer was 3.32. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.68 (95% CI: 0.55, 0.85) for men and 0.49 (95% CI: 0.34, 0.69) for women.

The incidence of breast cancer among women was 3.63 and increased with age. Although the IR was notably higher among women with endometrial polyps (IR 7.56), this IR is based on only 4 cases among women with polyps. When restricted to the population age 65 years and older, the IR of breast cancer was 5.72. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.94 (95% CI: 0.82, 1.06).

The incidence of colon/rectum cancer was 0.70 and increased with age. When restricted to the population age 65 years and older, the IR of colon/rectum cancer was 1.60. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.82 (95% CI: 0.53, 1.28) for men and 0.75 (95% CI: 0.54, 1.04) for women.

The incidence of kidney/renal cancer was 0.41 and higher among men (0.87 vs. 0.26) and patients with renal impairment or dialysis (2.36). When restricted to the population age 65 years and older, the IR of kidney cancer was 0.73. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.98 (95% CI: 0.61, 1.59) for men and 0.63 (95% CI: 0.38, 1.04) for women.

The incidence of cancer of the lung/bronchus was 0.84 and higher among men (1.30 vs. 0.70) and patients with claims-based evidence of alcohol abuse (3.96 vs. 0.83). When restricted to the population age 65 years and older, the IR of lung and bronchus cancer was 2.11. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.87 (95% CI: 0.59, 1.29) for men and 0.70 (95% CI: 0.52, 0.94) for women.

The incidence of melanoma was 0.23, increased with age, and was higher among men (0.39 vs. 0.19). When restricted to the population age 65 years and older, the IR of melanoma was 0.40. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 1.17 (95% CI: 0.59, 2.34) for men and 0.89 (95% CI: 0.50, 1.57) for women.

The incidence of non-Hodgkin's lymphoma was 0.64, increased with age, and was higher among men (1.03 vs. 0.51). When restricted to the population age 65 years and older, the IR of non-Hodgkin's lymphoma was 1.24. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.91 (95% CI: 0.58, 1.43) for men and 0.94 (95% CI: 0.67, 1.30) for women.

The incidence of pancreatic cancer was 0.20 and was higher among patients with renal impairment/dialysis (0.82 vs. 0.19). When restricted to the population age 65 years and older, the IR of pancreatic cancer was 0.47. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 1.02 (95% CI: 0.47, 2.21) for men and 0.56 (95% CI: 0.29, 1.07) for women.

The incidence of prostate cancer was 14.93 and was higher among patients with claims evidence of smoking (22.92 vs. 14.70), COPD (19.86 vs. 14.77), and renal impairment/dialysis (19.86 vs. 14.77). When restricted to the population age 65 years and older, the IR of prostate cancer was 25.36. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.90 (95% CI: 0.80, 1.01).

The incidence of uterine cancer was 0.34, increased with age, and was higher among women with baseline claims for any cancer medications (0.91 vs. 0.31). This finding may suggest that women who already had cancer were at a higher risk for uterine cancer or that the algorithm to screen out prevalent uterine cancers did not identify all cases. When restricted to the population age 65 years and older, the IR of uterine cancer was 0.64. For all medications combined, the age-adjusted IRR for currently exposed person-time vs. currently unexposed person-time was 0.73 (95% CI: 0.48, 1.12).

7.4 Evaluation of Drug Use Patterns

Antimuscarinic medications were classified based on time since drug approval. Patient and provider characteristics were compared across newly approved medications (solifenacin, darifenacin, fesoterodine, trospium) vs. more established medications (oxybutynin, tolterodine) in Tables D1a and D1b. For newer medications, 35% of the index dispensings were prescribed by urologists. In contrast, 27% of the index dispensings for the more established medications were prescribed by a urologist. The distribution of patient baseline characteristics across the approval categories were similar with the exception that patients who received the newer medications as an index dispensing were more likely to have diagnoses of incontinence (29% vs. 18%) or OAB (11% vs. 6%).

Across CV and cancer outcomes, approximately one-quarter of the person-time was classified as currently drug-exposed. Within the currently exposed time, approximately equal time was assigned to tolterodine, oxybutynin and solifenacin, with the remaining quarter shared among darifenacin, fesoterodine and trospium (Tables B2 and C3). Approximately one-third of the person-time assigned to ever-exposed to oxybutynin and a similar proportion was assigned to ever-exposed to tolterodine (Table C4).

The total number of dispensings for antimuscarinic medications ranged from 1 to 162 per person (median=2, IQR: 1, 7, Table D2), resulting in approximately 60 days of exposure. Nearly 40% of patients had only one dispensing over the entire study period. Over the entire study period, 82.2% of patients had dispensings for only one antimuscarinic medication, while 14.4% switched to a single other antimuscarinic drug, and 3.4% received 3 or more antimuscarinics.

Table D2 provides information about the number of patients who switched medications over the study period as well as the intervals between unique medications. For all drugs, the median number of dispensings of the index drug prior to switching to another drug was 2. The median number of dispensings of the drug to which patients switched was 3 for index users of all drugs, except for solifenacin where the median was 2 dispensings. The median interval between the end of use of the index drug (based on days of use) and the initiation of a second drug ranged from 12 days for fesoterodine (IQR: -3 to 57 days, where a negative number indicates that the second drug was dispensed before the anticipated completion of the prior drug) to 40 days for oxybutynin (IQR: -1 to 198 days). For all index drug groups, the most common switch was to oxybutynin. For the oxybutynin index group, the most common switch was to tolterodine.

7.5 Positive Predictive Values

The validation of the CV, cancer and covariate algorithms was done in several steps, as outlined in the methods section:

- Case identification using originally- proposed algorithms;
- Medical chart review, case adjudication, and calculation of PPVs for each endpoint;

For CV only:

- Re-assessment of the algorithm through additional claims profile review
- Definition of revised algorithm and

- Calculation of revised PPVs to assess concordance between the algorithm and the adjudicated cases

The results of each step are described below.

7.5.1 PPV for AMI

The original algorithm for acute myocardial infarction (AMI) required at least one claim with an ICD-9 code of 410.xx (Acute Myocardial Infarction), in the primary or secondary position, from an emergency department or inpatient setting. There were 35 charts sought and 25 charts obtained for the adjudication of the AMI outcome. The results were: 16 confirmed cases, 6 non-cases and 3 questionable cases, resulting in a positive predictive value (PPV) of 64% (95% CI: 43%, 82%).

To identify an algorithm with more accurate case ascertainment, additional analyses were performed, resulting in two new exploratory algorithms. Algorithm A and B, which included classifications for “probable cases”, “possible cases,” and “non-cases” rather than just “confirmed” and “non-cases,” were applied to the remaining 22 patients with charts. The 3 charts that were adjudicated as “questionable” were excluded from the analysis due adjudicators’ comments suggesting there was insufficient information to evaluate case status. An additional 5 charts were excluded because the date of the medical services included in the chart obtained was at least one week prior to the suspected event date defined by the new algorithms. The final sample size was 17 charts.

Algorithm A included AMI ICD-9 codes and DRGs and classified 13 of the patients as probable cases, while 4 possible cases were identified. There were 0 non-cases identified, due to original criteria for selecting charts for adjudication.[§§§]

Algorithm B added revascularization codes to Algorithm A and also classified the same 13 patients as probable cases and the same 4 patients as possible cases. There were 0 non-cases identified due to original criteria for selecting charts for adjudication. Among the charts already obtained, no additional potential cases were identified through the addition of the revascularization codes into the algorithm.

The algorithms’ classifications were compared to the adjudicators’ results. For both algorithms, all of the claims-identified probable cases were classified as cases by the adjudicators, resulting in PPVs of 100% (13 of 13, Table E1). All of the four possible claims-identified cases were classified as non-cases by the adjudicators. This evidence informed the decision that only probable cases would be considered cases for the calculation of incidence rates presented in this report.

The additional step of profile review by the Principal Epidemiology Consultant (PEC) resulted in 8 (62%) of the 13 claims-identified probable cases being classified as confirmed cases by the

[§§§] The case definition for the selection of charts was determined early in the study process when the less stringent AMI and stroke algorithms were used.

claims-profile process. All of the 4 patients defined as possible cases by the algorithm were classified as non-cases by the PEC, in agreement with the clinical adjudicators.

7.5.2 PPV for Stroke

Initially, stroke was defined based on the presence of hospital diagnosis codes 430, 431, 433.x1, 434.x1 and 436, located in the first position only. There were 123 charts sought and 94 charts abstracted and the estimated PPV was 33% (data not shown). This low PPV was in large part due to the subgroup of claims-identified cases based on ICD-9 diagnosis code 436, which had a PPV of 0%. This code was changed in 2006 from "*Cerebrovascular accident*" to "*Acute, but ill-defined, cerebrovascular disease*" and therefore use of this code on claims occurring after 2006 resulted in inaccurate case ascertainment.

The revised algorithm**** that included ICD-9 diagnosis and procedure codes, medications, CPT codes and DRGs was applied to claims data for patients with already-adjudicated charts and there were 57 charts that fell within the appropriate time-window for review. Among this group, 32 patients were classified as probable cases according to the algorithm. Zero possible cases were identified and 25 non-cases were identified. The addition of stroke DRGs to the algorithm added one additional probable case to the 31 that were probable based only on ICD-9 and CPT codes.

Among the 32 claims-identified probable cases, 21 were classified as confirmed cases by the adjudicators (PPV = 66%). Among the 11 claims-identified probable cases that were classified as non-cases by the adjudicators, all 11 patients had claims for diagnostic scans, 4 patients had claims with hemorrhagic codes, 7 patients had claims for ischemic codes, one had medications after the claims date for stroke, 3 patients had claims indicating post-stroke therapies, and 3 patients had stroke DRGs. No deaths occurred in this group.

Among the 17 patients with a stroke DRG, 14 were adjudicator-confirmed cases (82%). However, of the 40 patients without a stroke DRG, 9 were adjudicator-confirmed cases, which suggests that relying only on DRGs would result in a substantial loss of true cases.

The additional claims profile review by the Principal Epidemiology Consultant classified 20 (63%) of the 32 claims-identified cases as confirmed cases. Of these 20 confirmed cases, 19 were also classified as confirmed by the clinical adjudicators. These findings also suggest that while the PPV for stroke was much lower than the AMI PPV, the agreement between the adjudicators and claims-profile review was very high (19/20), which also allows for a useful and timely claims-based estimate of the incidence of stroke before the completion of medical chart abstraction. Together, these algorithms and claims-profile review may be useful tools for early assessment of the safety of mirabegron.

**** Refer to Appendix 1 for details of the algorithms

7.5.3 PPVs for 10 Cancer Types

PPVs were calculated from approximately 30 charts for each of the 10 cancers and for a composite measure (n=305, Table E2) for all charts and stratified by baseline history of cancer. Among patients without baseline history of cancer, the PPVs ranged from a high of 100% for breast cancer to a low of 79% for lung. The composite PPV was 90% and improved to 91% when questionable cases were added to the numerator. Among patients with a baseline history of cancer, the PPVs ranged from a high of 100% for breast cancer, melanoma and uterine cancer to a low of 70% for pancreatic and kidney cancer. The composite PPV was 86% and improved to 89% when questionable cases were added to the numerator. There were no charts classified as having insufficient information to determine case status. Patients for whom cancer charts were obtained tended to be slightly younger than patients eligible for chart abstraction (9% >= age 65 years vs. 21% >= age 65 years) but other baseline characteristics were similar (Tables G3a, G3b).

7.5.4 PPVs for Potential Cancer Covariates

The PPVs for the potential cancer covariates are presented in Table E3.

The definition of diabetes required both a claim with diagnosis code for diabetes (250.x2 or 250.x0) as well as evidence of a dispensing for at least one antidiabetic medication. There were 3 charts with insufficient information and all of the 20 remaining claims-identified cases were confirmed, resulting in a PPV of 100%.

The definition of endometrial polyps required at least one claim with ICD-9 code 621.0. The PPV was 71% (22/31) when the 3 questionable cases were classified as non-cases and improved to 81% when the questionable cases were included in the numerator as cases.

The definition of irritable bowel syndrome required at least one claims with ICD-9 code 564.1. The PPV was 52% (12/23). There were no questionable cases, but when the 2 charts with comments suggesting insufficient information were excluded from the denominator, the PPV increased to 57%.

The definition of polycystic ovary syndrome required at least one claims with ICD-9 code 256.4. The PPV was 57% (13/23) when the 5 questionable cases were classified as non-cases and improved to 78% when the questionable cases were included in the numerator as cases. For most patients classified as questionable, the reviewer noted that confirmatory testing was not present in the charts.

7.6 Negative Predictive Values for 10 Cancer Types

As outlined in Table F1, a total of 298 charts were sought among patients who had at least one claim with a diagnosis of cancer any time during follow-up but who did not meet the more stringent case criteria. For most cancers, approximately 20 charts were obtained (total = 227). The NPV for the composite measure of all cancers was 33% (26%, 38%). The range of NPVs across 10 cancers was a low of 11% for prostate cancer and a high of 59% for lung cancer. When the questionable cases were removed from the numerator, the NPVs improved to a low of 15% for prostate cancer to a high of 73% for lung cancer. The cancer with the most number of

questionable cases was pancreatic cancer (8 non-cases, 5 questionable cases, 8 confirmed cases).

7.7 Availability of Covariate Data in the ORD and Medical Charts

Within the cohort, the baseline prevalence of some potential confounders were reported from claims-based definitions: obesity (4%), alcohol abuse (0.5%), smoking (3%) and dementia (0.4%) (Table A1). For the cancer analyses, the baseline claims-based prevalence of key potential confounders for which chart abstraction was completed includes diabetes (9%), irritable bowel syndrome (2%), polycystic ovary disease (0.2%), and endometrial polyps (0.2%.)

The data abstracted from 119 charts obtained for patients with claims-identified stroke or AMI are summarized in Tables G1a, b.[††††] Distributions of abstracted variables are summarized by index drug group. Based on comments within the charts, weight was not classified in 75 charts (63%). There were 13 charts with actual values for BMI, 79 charts with values for weight and 58 charts with values for height. Smoking information was available for 86% of patients and among those with data, 17 patients (17%) were current smokers and 58 patients (57%) reported to be never/non-smokers. Only 3% of patients had data indicating history of treatment for alcohol abuse. There was frequent reporting of diabetes (35%), hypercholesterolemia (49%), and hypertension (74%).

The data abstracted from 305 charts obtained for patients with claims-identified cancers are summarized in Tables G2a, b. Distributions of abstracted variables are summarized by index drug group. Based on comments within the charts, weight was not classified in 64% of the charts. There were 35 charts with actual values for BMI, 119 with values for weight and 139 with values for height. Smoking information was available for 70% of patients, with 48.8% reported to be never/non-smokers. There were 4% of charts with information indicating history of treatment for alcohol abuse. There was frequent reporting of diabetes (15%).

7.8 Additional Data Analyses

Among the 4,612 patients whose first outcome was a diagnosis of one of the cancers of interest during follow-up, 100 patients had a MACE event as a second outcome (or in some cases, as a concurrent outcome) and 116 patients had claims-based evidence of all-cause mortality as a second or concurrent outcome (Table H1). Among the 3,067 patients who had a MACE event as a first outcome, 49 patients had a cancer diagnosis as a second or concurrent outcome. The most common overlap between outcomes was any MACE event followed by all-cause mortality (n=398). The median number of days between these events was 0 days (IQR: 0,18) with a mean of 108.4 days (range: 0-2,397). There were 51 patients who had an AMI followed next by

[††††] Note: The charts were obtained on patients identified using the original definition of AMI and stroke. Analysis of the chart-based findings resulted in modifications to the algorithms. The summary of chart abstracted data was re-run including patients who would have been identified as probable stroke or AMI (total n=62) and distributions were similar (data not shown).

a stroke and 31 patients who had a stroke followed next by an AMI. There were 101 patients who had an AMI followed next by CV death, and 52 stroke patients with a subsequent CV death.

Although not specified in the protocol, analyses to summarize chart procurement rates by site of service and outcome have been performed. The procurement rates were similar for cardiovascular, cancer, non-cancer (76%, 75%, 76% respectively), all of which were greater than the procurement rate for covariate validation (64%). This lower rate may be in part due to a higher proportion of charts requested from outpatient facilities rather than inpatient facilities due to the less severe health outcome in question (Table H2).

8. Discussion

The goal of the study was to demonstrate what pertinent information can be reliably obtained from the administrative database and the medical records and to describe medication use patterns, as a basis for post-marketing studies of mirabegron use. Characteristics of a population of initiators of antimuscarinic medications over the time period of 01 January 2004 – 30 September 2012 are reported, along with claims-identified IRs and IRRs of CV and cancer outcomes. Examination of medication use patterns, such as switching between antimuscarinics as well as use of newly approved vs. established medications are provided, as well as the availability of data for the identification of potential confounders. PPVs and NPVs based on medical chart adjudication also are presented.

A total of 205,423 initiators of antimuscarinic medications were identified, with the most commonly used antimuscarinics being oxybutynin and tolterodine. The vast majority of patients used only one type of antimuscarinic throughout the study, and many had only one dispensing. There is little evidence of combination therapy (i.e. concurrent use of multiple antimuscarinics). There were few differences in the patients who initiated use of each of the drugs, with the exception that the newly approved medications were more often prescribed by urologists (as opposed to OB/GYN and Family/GPs) and were more often prescribed to patients with a baseline diagnosis of OAB or incontinence. This pattern may be due to the fact that the physician needs to justify the use of the new and more expensive therapies by providing a more specific diagnosis and may reflect changes in prescribing patterns over time.

After adjustment for age and sex, the IRRs for each antimuscarinic and for all drugs combined, compared to unexposed person-time, did not suggest an elevated risk for AMI, CV death, CHD death and all-cause mortality. For the stroke outcome and for cerebrovascular death, the IRR for exposure to any OAB relative to non-exposure appear to be elevated for the combined rates from all medications and for exposure to solifenacin (cerebrovascular death only) or tolterodine (stroke only). A similar increase was seen for cerebrovascular death among the patients age 65 years and older. All of the IRRs were consistent with the reference group within the analyses restricted to patients defined as high CV risk.

An additional exploratory analysis was performed for each individual antimuscarinic medication with the reference defined as the incidence rate during the person-time among comparator drug exposure time, rather than unexposed person-time (e.g. the IR of AMI during current exposure to oxybutynin compared to the IR of AMI during all other currently exposed person-time).

Results have been added to Table B2. All previously noted elevated IRRs became null (i.e. the confidence interval included 1.0), and there was a new finding of an IRR of 1.24 for all-cause mortality and exposure to oxybutynin compared to exposure to any other antimuscarinic drug. Solifenacin use person-time had lower rates of AMI, all-cause mortality and any MACE events compared to use of any other OAB medication.

The incidence rates of cancer were similar when using a 6-month vs. 12-month exclusion criteria, suggesting that application of the cancer-definition algorithm over a 6-month look-back period is sufficient for excluding the majority of patients with claims-identifiable prevalent cancers during the baseline period. However, there is a substantially elevated IR 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. This study is not intended or designed to define biologically plausible periods of causality. The findings, however, should be interpreted with the following consideration. There may have been undetected pre-clinical cancer during the baseline period, which is more likely to be diagnosed early in the study. In addition, surveillance bias is possible in that there may be increased diagnosis around the time of cohort entry because patients with cancer-like symptoms are more likely to seek medical consultation. Finally, protopathic bias should be considered, i.e. urinary cancers may cause symptoms which are misinterpreted as overactive bladder symptom, leading to the inappropriate decision to prescribe antimuscarinics to patients who actually have urinary cancer.

None of the gender-specific age-adjusted estimates suggest elevated cancer rates (all drugs vs. unexposed person-time) for the all-age group analyses and those analyses restricted to patients 65 years or older. These results should be interpreted with the understanding that due to the study design, all cohort members were exposed to at least one of the antimuscarinic medications and therefore a comparison to unexposed person-time among patients who were never exposed to any antimuscarinic medications is not feasible in the current study data. While use of patients exposed to the same medication class as a reference group may attenuate the findings, the identification of an appropriate never-exposed comparison group would require extensive consideration of potential observed and unobserved confounders.

Issues of competing health risks, differences in access to health care, cancer screening, and geography, complicate comparing claims-based incidence rates to external references; however, it is interesting to note that incidence rates for both the CV and cancer outcomes tend to be lower but within the range of published findings in comparable populations.

The claims-based incidence rates of some of the CV events were usually lower than published rates in populations described in Core Common protocol #178-CL-114. For example, the claims-based incidence of AMI in our study population was 3.47/1,000 pys, as compared to 5.0/1,000 reported by Garcia Rodriguez.[15] However, our study population was younger and had a larger proportion of women. The claims-based incidence of stroke in our study population was 2.6/1,000 pys for women and 6.0/1,000 pys for men, as compared to 4.42/1,000 for women and 4.56/1,000 pys for men, as reported by Petrea.[16] In contrast, the incidence of CV death in our study population was 0.69/1,000 pys as compared to 1.67/1,000 pys as reported by Kochanek.[17] These differences may be a function of the age and health of the underlying insured population as well as limitations of claims-data to fully assess the timing and cause or mortality. The Core protocols for the main safety study for mirabegron (Protocol numbers: 178-

CL-113, 178-CL-114) include linkage to the National Death Index files for confirmation of date and cause of mortality.

For some cancers, claims-identified IRs also were similar to external comparisons. For example, the age-adjusted IRs among both sexes in the US SEER data, 2005-2009 (adjusted to the 2000 US standard population) is 0.63/1,000[13] for lung cancer, as compared to 0.84 /1,000 (claims based) in the ORD. In contrast, some cancers, such as breast cancer that is highly susceptible to screening bias, had higher rates within the ORD (3.63/1,000) as opposed to the SEER estimate of 0.67/1,000.

The PPVs for AMI and most cancers suggest that the estimated claims-based incidence rate accurately identifies patients who had disease that could be confirmed with medical charts. PPV estimation does not address the number of potential cases that were not identified in claims but which may be valid cases.

Although the final algorithm was not used to identify a new set of charts for additional adjudication, its performance was evaluated on a set of charts similar to those that would have selected had the process been repeated (i.e. the set of charts for patients identified as probable cases according to the new algorithm). While a PPV of 66% for stroke may suggest that the incidence rate may be overestimated, it also is possible that the claims-based algorithm also failed to identify other valid stroke cases, in which case the true incidence rate is underestimated. This study demonstrated that while the PPV for stroke was relatively low despite the complexity of the algorithm (i.e. consideration of diagnosis codes, DRGs, treatment and therapy for stroke), the agreement between the adjudicators and claims-profile review was very high, which may allow for a useful and timely claims-based estimate of the incidence of stroke before, or potentially instead of the completion of medical chart abstraction and adjudication. Chart adjudication has been included in the Core protocols (178-CL-113 and 114) and the addition of profile review to obtain more timely estimates of safety is under consideration for inclusion in the revised protocols. Together, these algorithms and claims-profile review may be useful tools for early assessment of the safety of mirabegron.

The definition of cancer required 2 or more claims with cancer-specific ICD-9 diagnosis codes, at least 30, but not more than 90 days apart. This algorithm was applied to the baseline data to identify prevalent cases and to the follow-up data to identify incident cases. The comparison to adjudicated results suggest that this stringent criteria did an excellent job of identifying potential cases, however, there is a trade-off given that this methodology may have misclassified too many true cases as non-cases among patients who had a cancer claim but did not meet the algorithm definition, thereby underestimating true cancer incidence. This underestimation is likely to be unrelated to the exposure of interest and therefore would not bias the relative risks but may have implication for projected sample size calculations and estimates cancer incidence.

An examination of the number of potential cases of cancer identified during the baseline period and within the first year after index dispensing underscores the importance of identifying the appropriate population for an analysis of incident cancer. Failure to exclude baseline cases, or cases that occur shortly after initiation of a medication, has the potential to adversely affect incidence estimation and inferences that can be drawn from the study. Few additional baseline cancer cases were identified when the baseline period was expanded to 12 months prior to

index rather than 6 months prior to index, suggesting the use of 6 months increases the available sample size and provides similar exclusions as the longer 12 month period.

The low baseline prevalence of conditions such obesity, reported alcohol abuse and smoking suggest that the claims data potentially underestimate the occurrence within the patient population. Collection of these and other characteristics on a subset of patients' medical charts provided additional information regarding height, weight , smoking status and use of low-dose aspirin (which would not be observed in claims data) for 50-66% of patients but provided information on alcohol abuse or treatment on less than 5% of patients.

Although the PPVs for some of the potential cancer covariates were low, the claims-based prevalence also was extremely low: endometrial polyps (0.2% among women), irritable bowel syndrome (1.8%) and polycystic ovary syndrome (0.2% among women) and therefore these characteristics cannot be strong confounders within this study population. Incidence rates for an array of sex-specific and composite outcome metrics were compared across individual drugs, combinations of drugs, and for unexposed person-time; therefore, individual estimates reported from this study should be interpreted with consideration of the vast number of comparisons included in these exploratory analyses. The information obtained from this validation study may be used to inform power calculations for the mirabegron Core studies and will help to define the *apriori* hypotheses to be tested. In particular, the observed duration of exposure, drug switching behaviors, the claims-based incidence rates of outcomes, and the characteristics of users of early adopters of newly-approved medications (potential confounders due to the association with exposure) are key elements that can be used to anticipate when the study population of new users and comparators will be sufficient for appropriate statistical analysis and inference.

9. Conclusion

The majority of the index dispensings were for tolterodine or oxybutynin, both of which were approved almost 10 years prior to the other antimuscarinic medications included in this report. Across all OAB medications, the median number of dispensings per person was 2, corresponding to approximately 60 days of exposure (plus a grace period). The claims-identified baseline characteristics of patients across index drug cohorts were similar, suggesting little confounding by these characteristics. The claims-identified incidence rates of CV and cancer outcomes were lower than external comparisons, which may be reflective of the health of a commercially insured population. IRs were higher among patients age 65 years and older and those identified as high risk for CV events. Based on claims-identified cases, there was an observed elevated incidence of stroke and incidence of cerebrovascular death among the person-time currently exposed to any antimuscarinic medication, relative to unexposed person-time. When comparisons were restricted to exposed-person time to other antimuscarinics, an elevated IRR was observed for all-cause mortality and exposure to oxybutynin. In contrast, decreased IRRs were observed for solifenacin use and risk of AMI and any MACE outcome and there was not a consistent pattern of increased or decreased incidence of the various outcomes across medications and comparison groups.

Of special relevance to the mirabegron safety program is the observation of substantially higher incidence of the composite measure of cancer, bladder cancers and prostate cancer during the

first 6 months after the index exposure relative to the longer intervals after initial exposure. These elevated rates suggest the existence of pre-clinical cancers upon study entry; surveillance bias and protopathic bias should be considered.

None of the age-adjusted analyses of claims-identified sex-specific cancer outcomes suggest an elevated incidence rate during current exposure to antimuscarinic medications as a group, as compared to unexposed person-time. In contrast, patients who were ever exposed to oxybutynin were observed to have higher incidence rates of any cancer (men and women) as compared to patients who were never exposed to oxybutynin. Similar findings were observed for bladder (men and women), lung (men only), and kidney cancers (women only).

Updating of published algorithms based on ICD-9 coding changes was essential for accurate identification of potential CV cases. A stringent case definition for cancer outcomes resulted in high PPVs, regardless of the patients' history of cancer. In contrast, very low NPVs were observed when evaluated on patients with evidence of cancer during follow-up but who did not meet the same stringent definition for cancer. The patients for whom cancer charts were obtained were representative of the larger sample of patients with cancer outcomes.

This information will provide guidance for the final design, statistical power and implementation of the Core protocols (Protocol numbers: 178-CL-113, 178-CL-114) to allow for a timely and scientifically valid evaluation of the safety of mirabegron regarding CV and cancer risk among users of antimuscarinic medications for treatment of OAB.

10. Tables

Table A1. Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Antimuscarinic Treatment Initiator Group, Optum Research Database: 01 January 2004 - 30 September 2012

	Oxybutynin N = 66,502		Tolterodine N = 67,101		Solifenacin N = 43,162		Darifenacin N = 17,945		Fesoterodine N = 3,963		Trospium N = 6,750		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age														
18-44	16,719	25.1	15,349	22.9	9,468	21.9	3,534	19.7	814	20.5	1,312	19.4	47,196	23.0
45-54	16,655	25.0	17,656	26.3	11,371	26.3	4,578	25.5	1,001	25.3	1,595	23.6	52,856	25.7
55-64	19,799	29.8	19,136	28.5	13,629	31.6	5,651	31.5	1,307	33.0	2,057	30.5	61,579	30.0
65-74	7,382	11.1	7,662	11.4	4,906	11.4	2,154	12.0	491	12.4	859	12.7	23,454	11.4
75+	5,947	8.9	7,298	10.9	3,788	8.8	2,028	11.3	350	8.8	927	13.7	20,338	9.9
Gender														
Female	45,279	68.1	51,017	76.0	32,694	75.8	13,535	75.4	2,911	73.5	4,702	69.7	150,138	73.1
Male	21,223	31.9	16,084	24.0	10,468	24.3	4,410	24.6	1,052	26.6	2,048	30.3	55,285	26.9
Region														
Midwest	16,256	24.4	15,066	22.5	9,438	21.9	3,902	21.7	853	21.5	1,595	23.6	47,110	22.9
Northeast	5,521	8.3	6,778	10.1	3,184	7.4	1,499	8.4	307	7.8	549	8.1	17,838	8.7
South	33,689	50.7	35,877	53.5	25,203	58.4	10,292	57.4	2,309	58.3	3,710	55.0	111,080	54.1
West	11,036	16.6	9,380	14.0	5,337	12.4	2,252	12.6	494	12.5	896	13.3	29,395	14.3
Year of Cohort Entry														
2004	9,934	14.9	12,335	18.4	0	0.0	0	0.0	0	0.0	305	4.5	22,574	11.0
2005	7,745	11.7	11,468	17.1	2,207	5.1	1,487	8.3	0	0.0	1,025	15.2	23,932	11.7
2006	6,529	9.8	11,921	17.8	4,857	11.3	3,251	18.1	0	0.0	776	11.5	27,334	13.3
2007	5,440	8.2	10,177	15.2	5,075	11.8	3,280	18.3	0	0.0	837	12.4	24,809	12.1
2008	7,303	11.0	9,935	14.8	6,459	15.0	3,010	16.8	0	0.0	1,356	20.1	28,063	13.7
2009	7,105	10.7	7,376	11.0	6,772	15.7	2,457	13.7	578	14.6	885	13.1	25,173	12.3
2010	8,188	12.3	1,936	2.9	6,748	15.6	1,910	10.6	1,314	33.2	732	10.8	20,828	10.1
2011	8,233	12.4	1,210	1.8	6,599	15.3	1,517	8.5	1,257	31.7	578	8.6	19,394	9.4
2012	6,025	9.1	743	1.1	4,445	10.3	1,033	5.8	814	20.5	256	3.8	13,316	6.5

* Baseline period began July 1, 2003.

Table A1. Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Antimuscarinic Treatment Initiator Group, Optum Research Database: 01 January 2004 - 30 September 2012

	Oxybutynin N = 66,502		Tolterodine N = 67,101		Solifenacin N = 43,162		Darifenacin N = 17,945		Fesoterodine N = 3,963		Trospium N = 6,750		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Incontinence														
Yes	11,777	17.7	12,849	19.2	12,107	28.1	5,148	28.7	1,327	33.5	2,131	31.6	45,339	22.1
No	54,725	82.3	54,252	80.9	31,055	72.0	12,797	71.3	2,636	66.5	4,619	68.4	160,084	77.9
Overactive Bladder														
Yes	3,723	5.6	4,246	6.3	4,723	10.9	2,015	11.2	584	14.7	766	11.4	16,057	7.8
No	62,779	94.4	62,855	93.7	38,439	89.1	15,930	88.8	3,379	85.3	5,984	88.7	189,366	92.2
Cardiovascular Disease														
Yes	4,824	7.3	4,753	7.1	2,887	6.7	1,367	7.6	270	6.8	588	8.7	14,689	7.2
No	61,678	92.8	62,348	92.9	40,275	93.3	16,578	92.4	3,693	93.2	6,162	91.3	190,734	92.9
Cerebrovascular Disease														
Yes	777	1.2	830	1.2	410	1.0	179	1.0	48	1.2	89	1.3	2,333	1.1
No	65,725	98.8	66,271	98.8	42,752	99.1	17,766	99.0	3,915	98.8	6,661	98.7	203,090	98.9
Coronary Artery Disease														
Yes	3,873	5.8	3,768	5.6	2,416	5.6	1,109	6.2	226	5.7	488	7.2	11,880	5.8
No	62,629	94.2	63,333	94.4	40,746	94.4	16,836	93.8	3,737	94.3	6,262	92.8	193,543	94.2
Angina														
Yes	498	0.8	585	0.9	329	0.8	140	0.8	25	0.6	49	0.7	1,626	0.8
No	66,004	99.3	66,516	99.1	42,833	99.2	17,805	99.2	3,938	99.4	6,701	99.3	203,797	99.2
Congestive Heart Failure														
Yes	1,314	2.0	1,403	2.1	686	1.6	348	1.9	59	1.5	142	2.1	3,952	1.9
No	65,188	98.0	65,698	97.9	42,476	98.4	17,597	98.1	3,904	98.5	6,608	97.9	201,471	98.1
Atrial Fibrillation														
Yes	1,624	2.4	1,572	2.3	976	2.3	471	2.6	90	2.3	203	3.0	4,936	2.4
No	64,878	97.6	65,529	97.7	42,186	97.7	17,474	97.4	3,873	97.7	6,547	97.0	200,487	97.6
Antiarrhythmic Medications														
Yes	12,468	18.8	12,373	18.4	7,862	18.2	3,491	19.5	746	18.8	1,389	20.6	38,329	18.7
No	54,034	81.3	54,728	81.6	35,300	81.8	14,454	80.6	3,217	81.2	5,361	79.4	167,094	81.3

* Baseline period began July 1, 2003.

Table A1. Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Antimuscarinic Treatment Initiator Group, Optum Research Database: 01 January 2004 - 30 September 2012

	Oxybutynin N = 66,502		Tolterodine N = 67,101		Solifenacin N = 43,162		Darifenacin N = 17,945		Fesoterodine N = 3,963		Trospium N = 6,750		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hypertension														
Yes	21,873	32.9	21,063	31.4	14,323	33.2	6,200	34.6	1,398	35.3	2,267	33.6	67,124	32.7
No	44,629	67.1	46,038	68.6	28,839	66.8	11,745	65.5	2,565	64.7	4,483	66.4	138,299	67.3
Antihypertensives														
Yes	28,049	42.2	28,384	42.3	18,367	42.6	7,996	44.6	1,739	43.9	3,026	44.8	87,561	42.6
No	38,453	57.8	38,717	57.7	24,795	57.5	9,949	55.4	2,224	56.1	3,724	55.2	117,862	57.4
Diabetes														
Yes	5,994	9.0	5,733	8.5	3,917	9.1	1,701	9.5	407	10.3	630	9.3	18,382	9.0
No	60,508	91.0	61,368	91.5	39,245	90.9	16,244	90.5	3,556	89.7	6,120	90.7	187,041	91.1
High CV Risk Composite														
Yes	32,009	48.1	31,896	47.5	20,777	48.1	9,038	50.4	1,975	49.8	3,425	50.7	99,120	48.3
No	34,493	51.9	35,205	52.5	22,385	51.9	8,907	49.6	1,988	50.2	3,325	49.3	106,303	51.8
Hyperlipidemia														
Yes	20,831	31.3	21,904	32.6	14,369	33.3	6,359	35.4	1,296	32.7	2,360	35.0	67,119	32.7
No	45,671	68.7	45,197	67.4	28,793	66.7	11,586	64.6	2,667	67.3	4,390	65.0	138,304	67.3
Ischemic Heart Disease, excluding AMI														
Yes	4,211	6.3	4,169	6.2	2,640	6.1	1,211	6.8	243	6.1	522	7.7	12,996	6.3
No	62,291	93.7	62,932	93.8	40,522	93.9	16,734	93.3	3,720	93.9	6,228	92.3	192,427	93.7
Acute Myocardial Infarction														
Yes	171	0.3	168	0.3	89	0.2	33	0.2	7	0.2	15	0.2	483	0.2
No	66,331	99.7	66,933	99.8	43,073	99.8	17,912	99.8	3,956	99.8	6,735	99.8	204,940	99.8
Stroke														
Yes	415	0.6	394	0.6	184	0.4	74	0.4	22	0.6	38	0.6	1,127	0.6
No	66,087	99.4	66,707	99.4	42,978	99.6	17,871	99.6	3,941	99.4	6,712	99.4	204,296	99.5
Hypertriglyceridemia														
Yes	480	0.7	391	0.6	313	0.7	117	0.7	20	0.5	53	0.8	1,374	0.7
No	66,022	99.3	66,710	99.4	42,849	99.3	17,828	99.4	3,943	99.5	6,697	99.2	204,049	99.3

Abbreviations: AMI, Acute Myocardial Infarction; CV, Cardiovascular Disease

* Baseline period began July 1, 2003.

Table A1. Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Antimuscarinic Treatment Initiator Group, Optum Research Database: 01 January 2004 - 30 September 2012

	Oxybutynin N = 66,502		Tolterodine N = 67,101		Solifenacin N = 43,162		Darifenacin N = 17,945		Fesoterodine N = 3,963		Trospium N = 6,750		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Organ Transplant														
Yes	487	0.7	253	0.4	129	0.3	39	0.2	16	0.4	23	0.3	947	0.5
No	66,015	99.3	66,848	99.6	43,033	99.7	17,906	99.8	3,947	99.6	6,727	99.7	204,476	99.5
Alcohol Abuse														
Yes	361	0.5	317	0.5	166	0.4	82	0.5	19	0.5	26	0.4	971	0.5
No	66,141	99.5	66,784	99.5	42,996	99.6	17,863	99.5	3,944	99.5	6,724	99.6	204,452	99.5
Smoking														
Yes	2,478	3.7	1,827	2.7	1,154	2.7	440	2.5	131	3.3	172	2.6	6,202	3.0
No	64,024	96.3	65,274	97.3	42,008	97.3	17,505	97.6	3,832	96.7	6,578	97.5	199,221	97.0
Overweight / Obesity														
Yes	3,225	4.9	2,529	3.8	2,047	4.7	770	4.3	238	6.0	269	4.0	9,078	4.4
No	63,277	95.2	64,572	96.2	41,115	95.3	17,175	95.7	3,725	94.0	6,481	96.0	196,345	95.6
Gout														
Yes	650	1.0	488	0.7	359	0.8	140	0.8	37	0.9	52	0.8	1,726	0.8
No	65,852	99.0	66,613	99.3	42,803	99.2	17,805	99.2	3,926	99.1	6,698	99.2	203,697	99.2
Rheumatoid Arthritis														
Yes	864	1.3	950	1.4	680	1.6	314	1.8	69	1.7	109	1.6	2,986	1.5
No	65,638	98.7	66,151	98.6	42,482	98.4	17,631	98.3	3,894	98.3	6,641	98.4	202,437	98.6
Dementia														
Yes	235	0.4	295	0.4	131	0.3	77	0.4	12	0.3	56	0.8	806	0.4
No	66,267	99.7	66,806	99.6	43,031	99.7	17,868	99.6	3,951	99.7	6,694	99.2	204,617	99.6
Peptic Ulcer Disease														
Yes	304	0.5	303	0.5	170	0.4	80	0.5	14	0.4	30	0.4	901	0.4
No	66,198	99.5	66,798	99.6	42,992	99.6	17,865	99.6	3,949	99.7	6,720	99.6	204,522	99.6
Chronic Obstructive Pulmonary Disease														
Yes	1,767	2.7	1,835	2.7	1,070	2.5	500	2.8	94	2.4	178	2.6	5,444	2.7
No	64,735	97.3	65,266	97.3	42,092	97.5	17,445	97.2	3,869	97.6	6,572	97.4	199,979	97.4

* Baseline period began July 1, 2003.

Table A1. Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Antimuscarinic Treatment Initiator Group, Optum Research Database: 01 January 2004 - 30 September 2012

	Oxybutynin N = 66,502		Tolterodine N = 67,101		Solifenacin N = 43,162		Darifenacin N = 17,945		Fesoterodine N = 3,963		Trospium N = 6,750		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Renal Impairment / Dialysis														
Yes	2,273	3.4	1,557	2.3	1,058	2.5	429	2.4	119	3.0	191	2.8	5,627	2.7
No	64,229	96.6	65,544	97.7	42,104	97.6	17,516	97.6	3,844	97.0	6,559	97.2	199,796	97.3
Open Heart Surgeries														
Yes	277	0.4	283	0.4	174	0.4	53	0.3	6	0.2	38	0.6	831	0.4
No	66,225	99.6	66,818	99.6	42,988	99.6	17,892	99.7	3,957	99.9	6,712	99.4	204,592	99.6
Hospitalization within 45 Days of Cohort Entry Date														
Yes	5,755	8.7	2,873	4.3	710	1.6	336	1.9	54	1.4	124	1.8	9,852	4.8
No	60,747	91.4	64,228	95.7	42,452	98.4	17,609	98.1	3,909	98.6	6,626	98.2	195,571	95.2
Cholesterol Lowering Therapies														
Yes	17,912	26.9	17,795	26.5	13,041	30.2	5,493	30.6	1,300	32.8	2,106	31.2	57,647	28.1
No	48,590	73.1	49,306	73.5	30,121	69.8	12,452	69.4	2,663	67.2	4,644	68.8	147,776	71.9
Any CV Drug†														
Yes	33,468	50.3	33,912	50.5	22,544	52.2	9,662	53.8	2,134	53.9	3,653	54.1	105,373	51.3
No	33,034	49.7	33,189	49.5	20,618	47.8	8,283	46.2	1,829	46.2	3,097	45.9	100,050	48.7
Any History of Cancer														
Yes	5,452	8.2	3,954	5.9	2,543	5.9	1,067	6.0	286	7.2	444	6.6	13,746	6.7
No	61,050	91.8	63,147	94.1	40,619	94.1	16,878	94.1	3,677	92.8	6,306	93.4	191,677	93.3
Endometrial Polyps (Women only)														
Yes	81	0.2	94	0.2	75	0.2	24	0.2	4	0.1	5	0.1	283	0.2
No	45,198	99.8	50,923	99.8	32,619	99.8	13,511	99.8	2,907	99.9	4,697	99.9	149,855	99.8
Irritable Bowel Syndrome														
Yes	1,221	1.8	1,240	1.9	796	1.8	364	2.0	79	2.0	144	2.1	3,844	1.9
No	65,281	98.2	65,861	98.2	42,366	98.2	17,581	98.0	3,884	98.0	6,606	97.9	201,579	98.1
Polycystic Ovary Syndrome (Women only)														
Yes	149	0.7	99	1.1	101	1.9	34	0.2	8	0.2	14	0.2	405	0.2
No	21,074	99.3	9,281	98.9	5,236	98.1	17,911	99.8	3,955	99.8	6,736	99.8	205,018	99.8

Abbreviations: CV, Cardiovascular Disease

* Baseline period began July 1, 2003.

† CV drugs include antihypertensive medications, cholesterol lowering therapies and antiarrhythmic medications.

Table A1. Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Antimuscarinic Treatment Initiator Group, Optum Research Database: 01 January 2004 - 30 September 2012

	Oxybutynin N = 66,502		Tolterodine N = 67,101		Solifenacin N = 43,162		Darifenacin N = 17,945		Fesoterodine N = 3,963		Trospium N = 6,750		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Any Cancer Drug														
Yes	3,021	4.5	3,386	5.1	2,005	4.7	930	5.2	202	5.1	323	4.8	9,867	4.8
No	63,481	95.5	63,715	95.0	41,157	95.4	17,015	94.8	3,761	94.9	6,427	95.2	195,556	95.2
Alkylating Agents														
Yes	75	0.1	68	0.1	13	0.0	9	0.1	2	0.1	8	0.1	175	0.1
No	66,427	99.9	67,033	99.9	43,149	100	17,936	100	3,961	100	6,742	99.9	205,248	99.9
Antimetabolites														
Yes	723	1.1	788	1.2	525	1.2	239	1.3	50	1.3	93	1.4	2,418	1.2
No	65,779	98.9	66,313	98.8	42,637	98.8	17,706	98.7	3,913	98.7	6,657	98.6	203,005	98.8
Antimicrotubule Agents														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No	66,502	100	67,101	100	43,162	100	17,945	100	3,963	100	6,750	100	205,423	100
Topoisomerase-active Agents														
Yes	7	0.0	5	0.0	2	0.0	1	0.0	0	0.0	1	0.0	16	0.0
No	66,495	100	67,096	100	43,160	100	17,944	100	3,963	100	6,749	100	205,407	100
Antineoplastic Antibiotics														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No	66,502	100	67,101	100	43,162	100	17,945	100	3,963	100	6,750	100	205,423	100
Endocrine Agents														
Yes	2,172	3.3	2,497	3.7	1,455	3.4	689	3.8	152	3.8	219	3.2	7,184	3.5
No	64,330	96.7	64,604	96.3	41,707	96.6	17,256	96.2	3,811	96.2	6,531	96.8	198,239	96.5
Biologically-directed Therapies														
Yes	62	0.1	60	0.1	29	0.1	9	0.1	4	0.1	9	0.1	173	0.1
No	66,440	99.9	67,041	99.9	43,133	99.9	17,936	100	3,959	99.9	6,741	99.9	205,250	99.9
Immune Therapies														
Yes	37	0.1	32	0.1	11	0.0	5	0.0	0	0.0	3	0.0	88	0.0
No	66,465	99.9	67,069	100	43,151	100	17,940	100	3,963	100	6,747	100	205,335	100
Miscellaneous Agents														
Yes	4	0.0	3	0.0	4	0.0	0	0.0	1	0.0	0	0.0	12	0.0
No	66,498	100	67,098	100	43,158	100	17,945	100	3,962	100	6,750	100	205,411	100

* Baseline period began July 1, 2003.

Table A1.1 Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Age Groups, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Age 18 - < 65 N = 161,631		Age ≥ 65 N = 43,792		Total N = 205,423	
	N	%	N	%	N	%
Age						
18-44	47,196	29.2	0	0.0	47,196	23.0
45-54	52,856	32.7	0	0.0	52,856	25.7
55-64	61,579	38.1	0	0.0	61,579	30.0
65-74	0	0.0	23,454	53.6	23,454	11.4
75+	0	0.0	20,338	46.4	20,338	9.9
Gender						
Female	123,564	76.5	26,574	60.7	150,138	73.1
Male	38,067	23.6	17,218	39.3	55,285	26.9
Region						
Midwest	37,786	23.4	9,324	21.3	47,110	22.9
Northeast	13,096	8.1	4,742	10.8	17,838	8.7
South	90,102	55.8	20,978	47.9	111,080	54.1
West	20,647	12.8	8,748	20.0	29,395	14.3
Year of Cohort Entry						
2004	18,109	11.2	4,465	10.2	22,574	11.0
2005	18,486	11.4	5,446	12.4	23,932	11.7
2006	21,431	13.3	5,903	13.5	27,334	13.3
2007	19,657	12.2	5,152	11.8	24,809	12.1
2008	20,647	12.8	7,416	16.9	28,063	13.7
2009	19,658	12.2	5,515	12.6	25,173	12.3
2010	17,021	10.5	3,807	8.7	20,828	10.1
2011	15,689	9.7	3,705	8.5	19,394	9.4
2012	10,933	6.8	2,383	5.4	13,316	6.5

* Baseline period began July 1, 2003.

Table A1.1 Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Age Groups, Optum Research Database: 01 January 2004 - 30 September 2012

	Age 18 - < 65 N = 161,631		Age ≥ 65 N = 43,792		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Incontinence						
Yes	34,813	21.5	10,526	24.0	45,339	22.1
No	126,818	78.5	33,266	76.0	160,084	77.9
Overactive Bladder						
Yes	12,934	8.0	3,123	7.1	16,057	7.8
No	148,697	92.0	40,669	92.9	189,366	92.2
Cardiovascular Disease						
Yes	6,126	3.8	8,563	19.6	14,689	7.2
No	155,505	96.2	35,229	80.5	190,734	92.9
Cerebrovascular Disease						
Yes	1,093	0.7	1,240	2.8	2,333	1.1
No	160,538	99.3	42,552	97.2	203,090	98.9
Coronary Artery Disease						
Yes	4,987	3.1	6,893	15.7	11,880	5.8
No	156,644	96.9	36,899	84.3	193,543	94.2
Angina						
Yes	930	0.6	696	1.6	1,626	0.8
No	160,701	99.4	43,096	98.4	203,797	99.2
Congestive Heart Failure						
Yes	1,315	0.8	2,637	6.0	3,952	1.9
No	160,316	99.2	41,155	94.0	201,471	98.1
Atrial Fibrillation						
Yes	1,314	0.8	3,622	8.3	4,936	2.4
No	160,317	99.2	40,170	91.7	200,487	97.6
Antiarrhythmic Medications						
Yes	21,772	13.5	16,557	37.8	38,329	18.7
No	139,859	86.5	27,235	62.2	167,094	81.3

* Baseline period began July 1, 2003.

Table A1.1 Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Age Groups, Optum Research Database: 01 January 2004 - 30 September 2012

	Age 18 - < 65 N = 161,631		Age ≥ 65 N = 43,792		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Hypertension						
Yes	43,108	26.7	24,016	54.8	67,124	32.7
No	118,523	73.3	19,776	45.2	138,299	67.3
Antihypertensives						
Yes	56,764	35.1	30,797	70.3	87,561	42.6
No	104,867	64.9	12,995	29.7	117,862	57.4
Diabetes						
Yes	11,758	7.3	6,624	15.1	18,382	9.0
No	149,873	92.7	37,168	84.9	187,041	91.1
High CV Risk Composite						
Yes	64,718	40.0	34,402	78.6	99,120	48.3
No	96,913	60.0	9,390	21.4	106,303	51.8
Hyperlipidemia						
Yes	45,003	27.8	22,116	50.5	67,119	32.7
No	116,628	72.2	21,676	49.5	138,304	67.3
Ischemic Heart Disease, excluding AMI						
Yes	5,670	3.5	7,326	16.7	12,996	6.3
No	155,961	96.5	36,466	83.3	192,427	93.7
Acute Myocardial Infarction						
Yes	231	0.1	252	0.6	483	0.2
No	161,400	99.9	43,540	99.4	204,940	99.8
Stroke						
Yes	579	0.4	548	1.3	1,127	0.6
No	161,052	99.6	43,244	98.8	204,296	99.5
Hypertriglyceridemia						
Yes	1,068	0.7	306	0.7	1,374	0.7
No	160,563	99.3	43,486	99.3	204,049	99.3

Abbreviations: AMI, Acute Myocardial Infarction; CV, Cardiovascular Disease

* Baseline period began July 1, 2003.

Table A1.1 Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Age Groups, Optum Research Database: 01 January 2004 - 30 September 2012

	Age 18 - < 65 N = 161,631		Age ≥ 65 N = 43,792		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Organ Transplant						
Yes	785	0.5	162	0.4	947	0.5
No	160,846	99.5	43,630	99.6	204,476	99.5
Alcohol Abuse						
Yes	790	0.5	181	0.4	971	0.5
No	160,841	99.5	43,611	99.6	204,452	99.5
Smoking						
Yes	5,405	3.3	797	1.8	6,202	3.0
No	156,226	96.7	42,995	98.2	199,221	97.0
Overweight / Obesity						
Yes	7,854	4.9	1,224	2.8	9,078	4.4
No	153,777	95.1	42,568	97.2	196,345	95.6
Gout						
Yes	1,037	0.6	689	1.6	1,726	0.8
No	160,594	99.4	43,103	98.4	203,697	99.2
Rheumatoid Arthritis						
Yes	2,033	1.3	953	2.2	2,986	1.5
No	159,598	98.7	42,839	97.8	202,437	98.6
Dementia						
Yes	92	0.1	714	1.6	806	0.4
No	161,539	99.9	43,078	98.4	204,617	99.6
Peptic Ulcer Disease						
Yes	582	0.4	319	0.7	901	0.4
No	161,049	99.6	43,473	99.3	204,522	99.6
Chronic Obstructive Pulmonary Disease						
Yes	2,604	1.6	2,840	6.5	5,444	2.7
No	159,027	98.4	40,952	93.5	199,979	97.4

* Baseline period began July 1, 2003.

Table A1.1 Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Age Groups, Optum Research Database: 01 January 2004 - 30 September 2012

	Age 18 - < 65 N = 161,631		Age ≥ 65 N = 43,792		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Renal Impairment / Dialysis						
Yes	2,907	1.8	2,720	6.2	5,627	2.7
No	158,724	98.2	41,072	93.8	199,796	97.3
Open Heart Surgeries						
Yes	471	0.3	360	0.8	831	0.4
No	161,160	99.7	43,432	99.2	204,592	99.6
Cholesterol Lowering Therapies						
Yes	36,607	22.7	21,040	48.1	57,647	28.1
No	125,024	77.4	22,752	52.0	147,776	71.9
Any CV Drug†						
Yes	70,400	43.6	34,973	79.9	105,373	51.3
No	91,231	56.4	8,819	20.1	100,050	48.7
Any History of Cancer						
Yes	8,603	5.3	5,143	11.7	13,746	6.7
No	153,028	94.7	38,649	88.3	191,677	93.3
Endometrial Polyps (Women only)						
Yes	262	0.2	21	0.1	283	0.2
No	123,302	99.8	26,553	99.9	149,855	99.8
Irritable Bowel Syndrome						
Yes	3,210	2.0	634	1.5	3,844	1.9
No	158,421	98.0	43,158	98.6	201,579	98.1
Polycystic Ovary Syndrome (Women only)						
Yes	404	0.3	1	0.0	405	0.3
No	123,160	99.7	26,573	100.0	149,733	99.7

Abbreviations: CV, Cardiovascular Disease

* Baseline period began July 1, 2003.

† CV drugs include antihypertensive medications, cholesterol lowering therapies and antiarrhythmic medications.

Table A1.1 Distribution of Claims-Identified Baseline* Patient Characteristics (Categorical) Across Age Groups, Optum Research Database: 01 January 2004 - 30 September 2012

	Age 18 - < 65 N = 161,631		Age ≥ 65 N = 43,792		Total N = 205,423	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Any Cancer Drug						
Yes	6,520	4.0	3,347	7.6	9,867	4.8
No	155,111	96.0	40,445	92.4	195,556	95.2
Alkylating Agents						
Yes	123	0.1	52	0.1	175	0.1
No	161,508	99.9	43,740	99.9	205,248	99.9
Antimetabolites						
Yes	1,600	1.0	818	1.9	2,418	1.2
No	160,031	99.0	42,974	98.1	203,005	98.8
Antimicrotubule Agents						
Yes	0	0.0	0	0.0	0	0.0
No	161,631	100.0	43,792	100.0	205,423	100.0
Topoisomerase-active Agents						
Yes	9	0.0	7	0.0	16	0.0
No	161,622	100.0	43,785	100.0	205,407	100.0
Antineoplastic Antibiotics						
Yes	0	0.0	0	0.0	0	0.0
No	161,631	100.0	43,792	100.0	205,423	100.0
Endocrine Agents						
Yes	4,733	2.9	2,451	5.6	7,184	3.5
No	156,898	97.1	41,341	94.4	198,239	96.5
Biologically-directed Therapies						
Yes	123	0.1	50	0.1	173	0.1
No	161,508	99.9	43,742	99.9	205,250	99.9
Immune Therapies						
Yes	51	0.0	37	0.1	88	0.0
No	161,580	100.0	43,755	99.9	205,335	100.0
Miscellaneous Agents						
Yes	10	0.0	2	0.0	12	0.0
No	161,621	100.0	43,790	100.0	205,411	100.0

* Baseline period began July 1, 2003.

Table A2. Distribution of Claims-Identified Baseline* Patient Characteristics (Continuous) Across Antimuscarinic Treatment Initiator Groups, Optum Research Database: 01 January 2004 - 30 September 2012

	Oxybutynin N = 66,502		Tolterodine N = 67,101		Solifenacin N = 43,162		Darifenacin N = 17,945		Fesoterodine N = 3,963		Trospium N = 6,750		Total N = 205,423	
Baseline Characteristic	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Membership† Length (Months)	28	(14 - 50)	29	(15 - 49)	31	(16 - 58)	28	(14 - 52)	37	(18 - 64)	29	(15 - 52)	29	(15 - 52)
Number of Days in Hospital During Baseline (Entire Cohort)	0	(0 - 0)	0	(0 - 0)	0	(0 - 0)	0	(0 - 0)	0	(0 - 0)	0	(0 - 0)	0	(0 - 0)
Number of Days in Hospital During Baseline (Among Patients with at least 1 Day, N=28,269)	3	(2 - 6)	3	(2 - 7)	3	(2 - 6)	3	(2 - 6)	3	(1 - 6)	3	(2 - 6)	3	(2 - 6)
Total Health Care Costs ($)	3,480	(1,263 - 10,183)	2,582	(1,114 - 6,477)	3,014	(1,389 - 6,992)	3,005	(1,425 - 6,827)	3,537	(1,633 - 8,079)	3,633	(1,732 - 7,804)	3,008	(1,269 - 7,776)
Total Drug Costs ($)	591	(200 - 1,480)	732	(299 - 1,610)	837	(351 - 1,845)	894	(370 - 1,902)	990	(398 - 2,246)	1,031	(403 - 2,204)	733	(284 - 1,677)
Number of Unique ICD-9 Diagnosis Codes in Baseline (3-Digit Level)	26	(15 - 42)	28	(16 - 46)	26	(15 - 40)	28	(17 - 45)	22	(14 - 35)	31	(18 - 48)	27	(16 - 43)
Number of Unique Drugs Dispensed in Baseline (HICL Level)	7	(4 - 11)	7	(4 - 11)	7	(4 - 11)	7	(4 - 11)	8	(5 - 11)	8	(5 - 12)	7	(4 - 11)
Number of Unique Laboratory Tests in Baseline	11	(5 - 21)	12	(5 - 22)	11	(5 - 20)	12	(5 - 21)	10	(5 - 18)	12	(6 - 23)	11	(5 - 21)

Abbreviations: HICL, Hierarchical Ingredient Code List; IQR, Interquartile Range

* Baseline period began July 1, 2003.

† Membership from start of enrollment through index date

Table A2.1. Distribution of Claims-Identified Baseline* Patient Characteristics (Continuous) Across Age Groups, Optum Research Database: 01 January 2004 - 30 September 2012

	Age 18 - < 65 years N = 161,631		Age ≥ 65 years N = 43,792		Total N = 205,423	
Baseline Characteristic	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Membership† Length (Months)	27	(14 - 49)	36	(19 - 60)	29	(15 - 52)
Number of Days in Hospital During Baseline (Entire Cohort)	0	(0 - 0)	0	(0 - 0)	0	(0 - 0)
Number of Days in Hospital During Baseline (Among Patients with at least 1 Day, N=28,269)	3	(2 - 5)	4	(2 - 10)	3	(2 - 6)
Total Health Care Costs ($)	3,101	(1,225 - 8,687)	2,798	(1,418 - 5,334)	3,008	(1,269 - 7,776)
Total Drug Costs ($)	625	(251 - 1,460)	1,256	(548 - 2,333)	733	(284 - 1,677)
Number of Unique ICD-9 Diagnosis Codes in Baseline (3-Digit Level)	25	(15 - 40)	35	(21 - 55)	27	(16 - 43)
Number of Unique Drugs Dispensed in Baseline (HICL Level)	7	(4 - 10)	9	(6 - 13)	7	(4 - 11)
Number of Unique Laboratory Tests in Baseline	13	(7 - 23)	6	(2 - 12)	11	(5 - 21)

Abbreviations: HICL, Hierarchical Ingredient Code List; IQR, Interquartile Range

* Baseline period began July 1, 2003.

† Membership from start of enrollment through index date

Table A3.1. Top 25 Most Frequently Recorded Diagnoses Appearing in Claims During the 6-Month Baseline Period*, Optum Research Database: 01 January 2004 - 30 September 2012

3-Digit ICD-9 Diagnosis Code	Description	Total N = 205,423		
		N	%	Rank
788	Symptoms Involving Urinary System	105,745	51.5	1
V72	Special Investigations and Examinations	74,969	36.5	2
401	Essential Hypertension	74,199	36.1	3
272	Disorders of Lipoid Metabolism	69,056	33.6	4
599	Other Disorders of Urethra and Urinary Tract	63,209	30.8	5
V76	Special Screening for Malignant Neoplasms	58,973	28.7	6
780	General Symptoms	54,655	26.6	7
786	Symptoms Involving Respiratory System and Other Chest Symptoms	41,844	20.4	8
789	Other Symptoms Involving Abdomen and Pelvis	39,828	19.4	9
724	Other and Unspecified Disorders of Back	37,702	18.4	10
719	Other and Unspecified Disorders of Joint	35,696	17.4	11
729	Other Disorders of Soft Tissues	33,488	16.3	12
V58	Encounter for Other and Unspecified Procedure and Aftercare	32,916	16.0	13
596	Other Disorders of Bladder	32,663	15.9	14
625	Pain and Other Symptoms Associated with Female Genital Organs	30,307	14.8	15
V70	General Medical Examination	29,268	14.2	16
250	Diabetes Mellitus	28,738	14.0	17
530	Diseases of Esophagus	26,277	12.8	18
715	Osteoarthrosis and Allied Disorders	24,171	11.8	19
244	Acquired Hypothyroidism	22,953	11.2	20
787	Symptoms Involving Digestive System	22,796	11.1	21
790	Nonspecific Findings On Examination of Blood	21,274	10.4	22
600	Hyperplasia of Prostate	20,459	10.0	23
477	Allergic Rhinitis	19,188	9.3	24
592	Calculus of Kidney and Ureter	18,342	8.9	25

*Index day (date of cohort entry due to Antimuscarinic drug use) is included in the baseline period. Baseline period began July 1, 2003.

Table A3.2. Top 25 Most Frequently Recorded Procedures Appearing in Claims During the 6-Month Baseline Period*, Optum Research Database: 01 January 2004 - 30 September 2012

		Total		
		N = 205,423		
Code	Description	N	%	Rank
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity. Counseling and coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Typically, 15 minutes are spent face-to-face with the patient and/or family.	148,311	72.2	1
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Typically, 25 minutes are spent face-to-face with the patient and/or family.	121,969	59.4	2
36415	Collection of venous blood by venipuncture	81,822	39.8	3
80061	Lipid panel This panel must include the following: Cholesterol, serum, total (82465) Lipoprotein, direct measurement, high density cholesterol (HDL cholesterol) (83718) Triglycerides (84478)	64,203	31.3	4
76499	Unlisted diagnostic radiographic procedure	57,322	27.9	5
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	51,764	25.2	6
80053	Comprehensive metabolic panel. This panel must include the following: Albumin (82040) Bilirubin, total (82247) Calcium, total (82310) Carbon dioxide (bicarbonate) (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Phosphatase, alkaline (84075) Potassium (84132) Protein, total (84155) Sodium (84295) Transferase, alanine amino (ALT) (SGPT) (84460) Transferase, aspartate amino (AST) (SGOT) (84450) Urea nitrogen (BUN) (84520)	48,965	23.8	7
81002	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; non-automated, without microscopy	48,665	23.7	8

*Index day (date of cohort entry due to Antimuscarinic drug use) is included in the baseline period. Baseline period began July 1, 2003.

Table A3.2. Top 25 Most Frequently Recorded Procedures Appearing in Claims During the 6-Month Baseline Period*, Optum Research Database: 01 January 2004 - 30 September 2012

		Total		
		N = 205,423		
Code	Description	N	%	Rank
99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Typically, 10 minutes are spent face-to-face with the patient and/or family.	48,206	23.5	9
87086	Culture, bacterial; quantitative colony count, urine	43,463	21.2	10
81000	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; non-automated, with microscopy	42,276	20.6	11
89240	Unlisted miscellaneous pathology test	39,850	19.4	12
99396	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	38,322	18.7	13
81001	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; automated, with microscopy	37,531	18.3	14
81003	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity,	36,680	17.9	15
88305	Level IV - Surgical pathology, gross and microscopic examination biopsy	35,170	17.1	16
99244	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Typically, 60 minutes are spent face-to-face with the patient and/or family.	34,611	16.8	17

*Index day (date of cohort entry due to Antimuscarinic drug use) is included in the baseline period. Baseline period began July 1, 2003.

Table A3.2. Top 25 Most Frequently Recorded Procedures Appearing in Claims During the 6-Month Baseline Period*, Optum Research Database: 01 January 2004 - 30 September 2012

		Total		
		N = 205,423		
Code	Description	N	%	Rank
99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history; A detailed examination; Medical decision making of low complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Typically, 30 minutes are spent face-to-face with the patient and/or family.	34,033	16.6	18
71020	Radiologic examination, chest, two views, frontal and lateral	33,023	16.1	19
80050	General health panel This panel must include the following: Comprehensive metabolic panel (80053) Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Thyroid stimulating hormone (TSH) (84443)	31,768	15.5	20
93000	Electrocardiogram, routine ECG with at least 12 leads; with interpretation and report	31,601	15.4	21
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Typically, 40 minutes are spent face-to-face with the patient and/or family.	28,698	14.0	22
84443	Thyroid stimulating hormone (TSH)	28,032	13.6	23
99243	Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Typically, 40 minutes are spent face-to-face with the patient and/or family.	27,127	13.2	24

*Index day (date of cohort entry due to Antimuscarinic drug use) is included in the baseline period. Baseline period began July 1, 2003.

Table A3.2. Top 25 Most Frequently Recorded Procedures Appearing in Claims During the 6-Month Baseline Period*, Optum Research Database: 01 January 2004 - 30 September 2012

		Total		
		N = 205,423		
Code	Description	N	%	Rank
99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Typically, 45 minutes are spent face-to-face with the patient and/or family.	25,623	12.5	25

*Index day (date of cohort entry due to Antimuscarinic drug use) is included in the baseline period. Baseline period began July 1, 2003.

Table A3.3. Top 25 Most Frequently Recorded Medication Dispensings (AHFS Therapeutic Class) Appearing in Claims During the 6-Month Baseline Period*, Optum Research Database: 01 January 2004 - 30 September 2012

		Total		
		N = 205,423		
Code	Description	N	%	Rank
86120000	Genitourinary Smooth Muscle Relaxants	205,423	100	1
28080800	Opiate Agonists	80,347	39.1	2
8121800	Quinolones	56,779	27.6	3
24060800	HMG-CoA Reductase Inhibitors	47,311	23.0	4
28160400	Antidepressants	41,423	20.2	5
56283600	Proton-Pump Inhibitors	34,386	16.7	6
24240000	Beta-Adrenergic Blocking Agents	33,149	16.1	7
28080400	Nonsteroidal Anti-Inflammatory Agents	30,924	15.1	8
28240800	Benzodiazepines (Anxiolytic,Sedativ/Hyp)	30,459	14.8	9
24320400	Angiotensin-Converting Enzyme Inhibitors	29,819	14.5	10
68160400	Estrogens	28,499	13.9	11
92000000	Unclassified Therapeutic Agents	27,954	13.6	12
68360400	Thyroid Agents	26,948	13.1	13
68040000	Adrenals	25,957	12.6	14
8360000	Urinary Anti-Infectives	23,436	11.4	15
28249200	Anxiolytics, Sedatives & Hypnotics,Misc.	23,201	11.3	16
52080800	Corticosteroids (EENT)	21,876	10.6	17
24320800	Angiotensin II Receptor Antagonists	21,551	10.5	18
84080000	Antipruritics And Local Anesthetics	19,864	9.7	19
8122000	Sulfonamides (Systemic)	19,779	9.6	20
28129200	Anticonvulsants, Miscellaneous	19,674	9.6	21
8121600	Penicillins	18,422	9.0	22
48080000	Antitussives	18,301	8.9	23
8121200	Macrolides	18,152	8.8	24
84060000	Anti-Inflammatory Agents (Skin & Mucous)	17,618	8.6	25

Abbreviations: AHFS, American Hospital Formulary Service

*Index day (date of cohort entry due to Antimuscarinic drug use) is included in the baseline period. Baseline period began July 1, 2003.

Table A4. Length of Continuous Enrollment (Months) Among Initiators of Antimuscarinic Medications, Optum Research Database: 01 January 2004 - 30 September 2012

	N	Start of Enrollment Until Index Date* Median (IQR)	Index Date Through End of Enrollment Median (IQR)	Start of Enrollment to End of Enrollment Median (IQR)
All	205,423	29 (15 - 52)	19 (8 - 38)	58 (36 - 87)
Age Group (years)				
18-44	47,196	24 (13 - 43)	17 (7 - 35)	48 (28 - 76)
45-54	52,856	27 (14 - 49)	20 (8 - 39)	57 (34 - 86)
55-64	61,579	30 (15 - 54)	20 (8 - 38)	60 (36 - 87)
65-74	23,454	35 (18 - 59)	19 (8 - 38)	66 (36 - 93)
75+	20,338	38 (20 - 60)	23 (11 - 44)	72 (43 - 93)
Age Group (2 categories)				
18 - < 65 years	161,631	27 (14 - 49)	19 (8 - 37)	56 (33 - 84)
65+ years	43,792	36 (19 - 60)	21 (9 - 41)	69 (36 - 93)
History of Cancer During or Before Baseline Period[†]				
Yes	13,746	35 (18 - 61)	19 (8 - 36)	63 (36 - 93)
No	191,677	29 (15 - 51)	19 (8 - 38)	57 (36 - 87)
Occurrence of One or More of Top 10 Cancers During the Follow-Up Period[†]				
Yes	8,603	35 (18 - 58)	25 (13 - 47)	69 (45 - 96)
No	196,820	29 (15 - 52)	19 (8 - 38)	57 (35 - 87)
Occurrence of AMI or Stroke During the Follow-Up Period				
Yes	2,937	33 (17 - 54)	37 (21 - 59)	78 (54 - 103)
No	202,486	29 (15 - 52)	19 (8 - 38)	57 (36 - 87)

Abbreviations: AMI, Acute Myocardial Infarction; IQR, Interquartile Range

* Index date - date of initiation of any antimuscarinic medication. Baseline period began July 1, 2003.

[†] Based on claims data only. The top 10 cancers in males include prostate, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, Non-hodgkin's lymphoma, kidney and renal pelvis, and pancreas. The top 10 cancers in females include breast, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, uterusi, and pancreas.

Table A5a. Comparison of Patient Characteristics (Categorical) of Patients With Dispensings for Patches, Gels, or Syrups versus Tablets.
Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Patients who used Gels, Patches, Syrups N = 9,733		Patients who Used Tablets N = 195,690	
	N	%	N	%
Prescriber Category for Index Dispensing				
Urology	3,307	34.0	58,454	29.9
Family/General Practice	2,171	22.3	60,585	31.0
OB/GYN	2,157	22.2	26,986	13.8
Miscellaneous/Unknown	2,098	21.6	49,665	25.4
Age				
18-44	1,708	17.6	45,488	23.2
45-54	2,415	24.8	50,441	25.8
55-64	2,897	29.8	58,682	30.0
65-74	1,298	13.3	22,156	11.3
75+	1,415	14.5	18,923	9.7
Gender				
Female	8,297	85.3	141,841	72.5
Male	1,436	14.8	53,849	27.5
Region				
Midwest	1,821	18.7	45,289	23.1
Northeast	1,079	11.1	16,759	8.6
South	5,461	56.1	105,619	54.0
West	1,372	14.1	28,023	14.3
Year of Cohort Entry				
2004	2,258	23.2	20,316	10.4
2005	1,454	14.9	22,478	11.5
2006	1,284	13.2	26,050	13.3
2007	963	9.9	23,846	12.2
2008	1,032	10.6	27,031	13.8
2009	893	9.2	24,280	12.4
2010	796	8.2	20,032	10.2
2011	666	6.8	18,728	9.6
2012	387	4.0	12,929	6.6
Incontinence				
Yes	3,067	31.5	42,272	21.6
No	6,666	68.5	153,418	78.4
Overactive Bladder				
Yes	967	9.9	15,090	7.7
No	8,766	90.1	180,600	92.3

* Baseline period began July 1, 2003.

Table A5b. Comparison of Patient Characteristics (Continuous) of Patients With Dispensings for Patches, Gels or Syrups versus Tablets. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Gels, Patches, Syrups N = 9,733		Remainder of Cohort N = 195,690	
	Median	IQR	Median	IQR
Membership† Length (Months)	29	(15 - 49)	29	(15 - 52)
Number of Days in Hospital During Baseline	0	(0 - 0)	0	(0 - 0)
Total Health Care Costs ($)	3,017	(1,414 - 6,531)	3,008	(1,260 - 7,845)
Total Drug Costs ($)	1,008	(421 - 2,108)	721	(279 - 1,655)
Number of Unique ICD-9 DX Codes in Baseline (3-Digit Level)	35	(20 - 55)	27	(15 - 43)
Number of Unique Drugs Dispensed in Baseline (HICL Level)	8	(5 - 12)	7	(4 - 11)
Number of Unique Laboratory Tests in Baseline	13	(6 - 24)	11	(5 - 21)

Abbreviations: HICL, Hierarchical Ingredient Code List; IQR, Interquartile Range

* Baseline period began July 1, 2003.

† Membership from start of health plan enrollment through index date

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	AMI[†]			Stroke[‡]			CV Death		
	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]
Overall	1,535	442,646	3.47	1,474	442,603	3.33	308	444,948	0.69
Age									
18-44	40	94,299	0.42	71	94,269	0.75	3	94,370	0.03
45-54	164	117,567	1.39	184	117,537	1.57	19	117,828	0.16
55-64	458	131,536	3.48	393	131,642	2.99	58	132,279	0.44
65-74	302	49,819	6.06	285	49,832	5.72	54	50,291	1.07
75+	571	49,425	11.55	541	49,322	10.97	174	50,180	3.47
Gender									
Female	846	326,862	2.59	1,006	326,414	3.08	171	328,107	0.52
Male	689	115,784	5.95	468	116,189	4.03	137	116,840	1.17
Incontinence									
Yes	321	95,121	3.37	401	94,943	4.22	76	95,566	0.80
No	1,214	347,525	3.49	1,073	347,659	3.09	232	349,382	0.66
Overactive Bladder									
Yes	121	32,769	3.69	94	32,809	2.87	25	32,946	0.76
No	1,414	409,877	3.45	1,380	409,793	3.37	283	412,002	0.69
Cardiovascular Disease									
Yes	463	30,345	15.26	259	30,609	8.46	144	31,017	4.64
No	1,072	412,301	2.60	1,215	411,994	2.95	164	413,931	0.40
Cerebrovascular Disease									
Yes	59	4,577	12.89	49	4,613	10.62	10	4,675	2.14
No	1,476	438,069	3.37	1,425	437,990	3.25	298	440,273	0.68
Coronary Artery Disease									
Yes	398	24,744	16.08	216	24,973	8.65	121	25,322	4.78
No	1,137	417,902	2.72	1,258	417,630	3.01	187	419,626	0.45
Angina									
Yes	48	3,498	13.72	43	3,496	12.30	10	3,575	2.80
No	1,487	439,148	3.39	1,431	439,107	3.26	298	441,372	0.68

Abbreviations: AMI, Myocardial Infarction; CV, Cardiovascular Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] AMI based on "Algorithm B category = 1, probable case" which includes diagnosis codes, revascularization codes and DRGs.

[‡] Stroke based on the stroke algorithm category =1 , probable case

[§] IR: Incidence Rate per 1,000 person-years

[¶] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	AMI[†]			Stroke[‡]			CV Death		
	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]
Congestive Heart Failure									
Yes	133	7,537	17.65	79	7,605	10.39	62	7,717	8.03
No	1,402	435,109	3.22	1,395	434,998	3.21	246	437,231	0.56
Atrial Fibrillation									
Yes	116	10,039	11.55	3	10,174	0.29	45	10,183	4.42
No	1,419	432,607	3.28	1,471	432,429	3.40	263	434,765	0.60
Antiarrhythmic Medications									
Yes	687	82,246	8.35	538	82,441	6.53	173	83,250	2.08
No	848	360,400	2.35	936	360,162	2.60	135	361,697	0.37
Hypertension									
Yes	899	140,902	6.38	798	140,925	5.66	200	142,208	1.41
No	636	301,744	2.11	676	301,678	2.24	108	302,740	0.36
Antihypertensives									
Yes	1,133	189,321	5.98	999	189,393	5.27	251	190,975	1.31
No	402	253,325	1.59	475	253,209	1.88	57	253,972	0.22
Diabetes									
Yes	358	36,980	9.68	273	37,075	7.36	80	37,478	2.13
No	1,177	405,666	2.90	1,201	405,527	2.96	228	407,470	0.56
High CV Risk Composite									
Yes	1,241	212,468	5.84	1,123	212,485	5.29	272	214,275	1.27
No	294	230,178	1.28	351	230,118	1.53	36	230,672	0.16
Hyperlipidemia									
Yes	821	149,064	5.51	711	149,179	4.77	174	150,329	1.16
No	714	293,582	2.43	763	293,424	2.60	134	294,619	0.45
Ischemic Heart Disease, excluding AMI									
Yes	415	27,127	15.30	235	27,360	8.59	125	27,737	4.51
No	1,120	415,519	2.70	1,239	415,242	2.98	183	417,210	0.44

Abbreviations: AMI, Acute Myocardial Infarction; CV, Cardiovascular Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] AMI based on "Algorithm B category = 1, probable case" which includes diagnosis codes, revascularization codes and DRGs.

[‡] Stroke based on the stroke algorithm category =1 , probable case

[§] IR: Incidence Rate per 1,000 person-years

[¶] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	AMI[†]			Stroke[‡]			CV Death		
	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]
Acute Myocardial Infarction									
Yes	42	852	49.28	9	897	10.03	6	912	6.58
No	1,493	441,794	3.38	1,465	441,705	3.32	302	444,036	0.68
Stroke									
Yes	24	2,063	11.63	0	2,112	0.00	4	2,112	1.89
No	1,511	440,583	3.43	1,474	440,490	3.35	304	442,835	0.69
Hypertriglyceridemia									
Yes	15	2,929	5.12	9	2,934	3.07	1	2,955	0.34
No	1,520	439,717	3.46	1,465	439,669	3.33	307	441,993	0.69
Organ Transplant									
Yes	9	1,843	4.88	10	1,840	5.44	1	1,854	0.54
No	1,526	440,803	3.46	1,464	440,763	3.32	307	443,093	0.69
Alcohol Abuse									
Yes	14	1,682	8.32	10	1,692	5.91	1	1,697	0.59
No	1,521	440,964	3.45	1,464	440,911	3.32	307	443,251	0.69
Smoking									
Yes	77	11,488	6.70	42	11,548	3.64	9	11,609	0.78
No	1,458	431,158	3.38	1,432	431,054	3.32	299	433,339	0.69
Overweight / Obesity									
Yes	68	17,274	3.94	67	17,273	3.88	10	17,390	0.58
No	1,467	425,372	3.45	1,407	425,329	3.31	298	427,558	0.70
Gout									
Yes	25	3,319	7.53	26	3,310	7.85	6	3,357	1.79
No	1,510	439,327	3.44	1,448	439,292	3.30	302	441,591	0.68
Rheumatoid Arthritis									
Yes	32	6,307	5.07	36	6,308	5.71	9	6,363	1.41
No	1,503	436,339	3.44	1,438	436,295	3.30	299	438,585	0.68
Dementia									
Yes	25	1,552	16.11	30	1,532	19.58	4	1,581	2.53
No	1,510	441,094	3.42	1,444	441,071	3.27	304	443,367	0.69

Abbreviations: AMI, Myocardial Infarction; CV, Cardiovascular Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] AMI based on "Algorithm B category = 1, probable case" which includes diagnosis codes, revascularization codes and DRGs.

[‡] Stroke based on the stroke algorithm category =1 , probable case

[§] IR: Incidence Rate per 1,000 person-years

[¶] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	AMI[†]			Stroke[‡]			CV Death		
	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]	Cases	Person-years[¶]	IR[§]
Peptic Ulcer Disease									
Yes	14	1,780	7.87	14	1,775	7.89	3	1,797	1.67
No	1,521	440,866	3.45	1,460	440,828	3.31	305	443,151	0.69
Chronic Obstructive Pulmonary									
Yes	135	10,563	12.78	86	10,626	8.09	46	10,740	4.28
No	1,400	432,083	3.24	1,388	431,976	3.21	262	434,207	0.60
Renal Impairment / Dialysis									
Yes	136	9,708	14.01	92	9,738	9.45	49	9,861	4.97
No	1,399	432,938	3.23	1,382	432,865	3.19	259	435,086	0.60
Open Heart Surgeries									
Yes	33	1,740	18.97	24	1,758	13.65	6	1,802	3.33
No	1,502	440,906	3.41	1,450	440,845	3.29	302	443,146	0.68
Cholesterol Lowering Therapies									
Yes	722	124,974	5.78	633	125,075	5.06	158	126,082	1.25
No	813	317,672	2.56	841	317,527	2.65	150	318,866	0.47
Any CV Drug									
Yes	1,249	228,439	5.47	1,110	228,530	4.86	268	230,283	1.16
No	286	214,207	1.34	364	214,073	1.70	40	214,664	0.19
Any History of Cancer									
Yes	173	28,073	6.16	87	28,188	3.09	33	28,298	1.17
No	1,362	414,573	3.29	1,387	414,415	3.35	275	416,650	0.66

Abbreviations: AMI, Acute Myocardial Infarction; CV, Cardiovascular Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] AMI based on "Algorithm B category = 1, probable case" which includes diagnosis codes, revascularization codes and DRGs.

[‡] Stroke based on the stroke algorithm category =1 , probable case

[§] IR: Incidence Rate per 1,000 person-years

[||] CV drugs include antihypertensive medications, cholesterol lowering therapies and antiarrhythmic medications.

[¶] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	CHD Death			Cerebrovascular Death			All Cause Mortality		
	Cases[†]	Person-years[‖]	IR[‡]	Cases[†]	Person-years[‖]	IR[‡]	Cases	Person-years[‖]	IR[‡]
Overall	268	444,948	0.60	60	444,948	0.13	1,769	444,948	3.98
Age									
18-44	1	94,370	0.01	2	94,370	0.02	68	94,370	0.72
45-54	14	117,828	0.12	8	117,828	0.07	176	117,828	1.49
55-64	50	132,279	0.38	13	132,279	0.10	451	132,279	3.41
65-74	48	50,291	0.95	8	50,291	0.16	314	50,291	6.24
75+	155	50,180	3.09	29	50,180	0.58	760	50,180	15.15
Gender									
Female	147	328,107	0.45	35	328,107	0.11	998	328,107	3.04
Male	121	116,840	1.04	25	116,840	0.21	771	116,840	6.60
Incontinence									
Yes	66	95,566	0.69	14	95,566	0.15	377	95,566	3.94
No	202	349,382	0.58	46	349,382	0.13	1,392	349,382	3.98
Overactive Bladder									
Yes	22	32,946	0.67	7	32,946	0.21	118	32,946	3.58
No	246	412,002	0.60	53	412,002	0.13	1,651	412,002	4.01
Cardiovascular Disease									
Yes	140	31,017	4.51	12	31,017	0.39	512	31,017	16.51
No	128	413,931	0.31	48	413,931	0.12	1,257	413,931	3.04
Cerebrovascular Disease									
Yes	10	4,675	2.14	1	4,675	0.21	75	4,675	16.04
No	258	440,273	0.59	59	440,273	0.13	1,694	440,273	3.85
Coronary Artery Disease									
Yes	119	25,322	4.70	9	25,322	0.36	361	25,322	14.26
No	149	419,626	0.36	51	419,626	0.12	1,408	419,626	3.36
Angina									
Yes	9	3,575	2.52	1	3,575	0.28	36	3,575	10.07
No	259	441,372	0.59	59	441,372	0.13	1,733	441,372	3.93
Congestive Heart Failure									
Yes	60	7,717	7.78	4	7,717	0.52	252	7,717	32.66
No	208	437,231	0.48	56	437,231	0.13	1,517	437,231	3.47

Abbreviations: CHD, Coronary Heart Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] A patient may be counted as a cerebrovascular death and a CHD death if both codes appear near the time of death.

[‡] IR: Incidence Rate per 1,000 person-years

[‖] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	CHD Death			Cerebrovascular Death			All Cause Mortality		
	Cases[†]	Person-years[‖]	IR[‡]	Cases[†]	Person-years[‖]	IR[‡]	Cases	Person-years[‖]	IR[‡]
Atrial Fibrillation									
Yes	45	10,183	4.42	0	10,183	0.00	225	10,183	22.10
No	223	434,765	0.51	60	434,765	0.14	1,544	434,765	3.55
Antiarrhythmic Medications									
Yes	159	83,250	1.91	25	83,250	0.30	777	83,250	9.33
No	109	361,697	0.30	35	361,697	0.10	992	361,697	2.74
Hypertension									
Yes	181	142,208	1.27	29	142,208	0.20	1,005	142,208	7.07
No	87	302,740	0.29	31	302,740	0.10	764	302,740	2.52
Antihypertensives									
Yes	225	190,975	1.18	41	190,975	0.21	1,288	190,975	6.74
No	43	253,972	0.17	19	253,972	0.07	481	253,972	1.89
Diabetes									
Yes	72	37,478	1.92	12	37,478	0.32	363	37,478	9.69
No	196	407,470	0.48	48	407,470	0.12	1,406	407,470	3.45
High CV Risk Composite									
Yes	243	214,275	1.13	48	214,275	0.22	1,427	214,275	6.66
No	25	230,672	0.11	12	230,672	0.05	342	230,672	1.48
Hyperlipidemia									
Yes	153	150,329	1.02	33	150,329	0.22	782	150,329	5.20
No	115	294,619	0.39	27	294,619	0.09	987	294,619	3.35
Ischemic Heart Disease, excluding AMI									
Yes	123	27,737	4.43	10	27,737	0.36	392	27,737	14.13
No	145	417,210	0.35	50	417,210	0.12	1,377	417,210	3.30
Acute Myocardial Infarction									
Yes	6	912	6.58	0	912	0.00	21	912	23.03
No	262	444,036	0.59	60	444,036	0.14	1,748	444,036	3.94
Stroke									
Yes	4	2,112	1.89	0	2,112	0.00	43	2,112	20.36
No	264	442,835	0.60	60	442,835	0.14	1,726	442,835	3.90

Abbreviations: AMI, Acute Myocardial Infarction; CHD, Coronary Heart Disease; CV, Cardiovascular Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] A patient may be counted as a cerebrovascular death and a CHD death if both codes appear near the time of death.

[‡] IR: Incidence Rate per 1,000 person-years

[‖] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	CHD Death			Cerebrovascular Death			All Cause Mortality		
	Cases[†]	Person-years[‖]	IR[‡]	Cases[†]	Person-years[‖]	IR[‡]	Cases	Person-years[‖]	IR[‡]
Hypertriglyceridemia									
Yes	1	2,955	0.34	0	2,955	0.00	6	2,955	2.03
No	267	441,993	0.60	60	441,993	0.14	1,763	441,993	3.99
Organ Transplant									
Yes	1	1,854	0.54	0	1,854	0.00	41	1,854	22.11
No	267	443,093	0.60	60	443,093	0.14	1,728	443,093	3.90
Alcohol Use / Abuse									
Yes	1	1,697	0.59	0	1,697	0.00	23	1,697	13.56
No	267	443,251	0.60	60	443,251	0.14	1,746	443,251	3.94
Smoking									
Yes	5	11,609	0.43	4	11,609	0.34	61	11,609	5.25
No	263	433,339	0.61	56	433,339	0.13	1,708	433,339	3.94
Overweight / Obesity									
Yes	9	17,390	0.52	2	17,390	0.12	84	17,390	4.83
No	259	427,558	0.61	58	427,558	0.14	1,685	427,558	3.94
Gout									
Yes	5	3,357	1.49	1	3,357	0.30	32	3,357	9.53
No	263	441,591	0.60	59	441,591	0.13	1,737	441,591	3.93
Rheumatoid Arthritis									
Yes	7	6,363	1.10	3	6,363	0.47	41	6,363	6.44
No	261	438,585	0.60	57	438,585	0.13	1,728	438,585	3.94
Dementia									
Yes	3	1,581	1.90	1	1,581	0.63	32	1,581	20.24
No	265	443,367	0.60	59	443,367	0.13	1,737	443,367	3.92
Peptic Ulcer Disease									
Yes	2	1,797	1.11	1	1,797	0.56	17	1,797	9.46
No	266	443,151	0.60	59	443,151	0.13	1,752	443,151	3.95
Chronic Obstructive Pulmonary									
Yes	42	10,740	3.91	8	10,740	0.74	216	10,740	20.11
No	226	434,207	0.52	52	434,207	0.12	1,553	434,207	3.58

Abbreviations: CHD, Coronary Heart Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] A patient may be counted as a cerebrovascular death and a CHD death if both codes appear near the time of death.

[‡] IR: Incidence Rate per 1,000 person-years

[‖] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	CHD Death			Cerebrovascular Death			All Cause Mortality		
	Cases[†]	Person-years[‖]	IR[‡]	Cases[†]	Person-years[‖]	IR[‡]	Cases	Person-years[‖]	IR[‡]
Renal Impairment / Dialysis									
Yes	47	9,861	4.77	2	9,861	0.20	248	9,861	25.15
No	221	435,086	0.51	58	435,086	0.13	1,521	435,086	3.50
Open Heart Surgeries									
Yes	6	1,802	3.33	0	1,802	0.00	23	1,802	12.76
No	262	443,146	0.59	60	443,146	0.14	1,746	443,146	3.94
Cholesterol Lowering Therapies									
Yes	141	126,082	1.12	28	126,082	0.22	699	126,082	5.54
No	127	318,866	0.40	32	318,866	0.10	1,070	318,866	3.36
Any CV Drug[§]									
Yes	237	230,283	1.03	48	230,283	0.21	1,395	230,283	6.06
No	31	214,664	0.14	12	214,664	0.06	374	214,664	1.74
Any History of Cancer									
Yes	30	28,298	1.06	4	28,298	0.14	327	28,298	11.56
No	238	416,650	0.57	56	416,650	0.13	1,442	416,650	3.46

Abbreviations: CHD, Coronary Heart Disease; CV, Cardiovascular Disease; IR, Incidence Rate

* Baseline period began July 1, 2003.

[†] A patient may be counted as a cerebrovascular death and a CHD death if both codes appear near the time of death.

[‡] IR: Incidence Rate per 1,000 person-years

[§] CV drugs include antihypertensive medications, cholesterol lowering therapies and antiarrhythmic medications.

[‖] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	Any MACE Outcome		
	Cases	Person-years[§]	IR[†]
Overall	3,067	440,379	6.96
Age			
18-44	110	94,199	1.17
45-54	349	117,291	2.98
55-64	846	130,920	6.46
65-74	597	49,384	12.09
75+	1,165	48,584	23.98
Gender			
Female	1,869	325,222	5.75
Male	1,198	115,156	10.40
Incontinence			
Yes	740	94,509	7.83
No	2,327	345,870	6.73
Overactive Bladder			
Yes	217	32,640	6.65
No	2,850	407,739	6.99
Cardiovascular Disease			
Yes	788	29,965	26.30
No	2,279	410,414	5.55
Cerebrovascular Disease			
Yes	110	4,516	24.36
No	2,957	435,862	6.78
Coronary Artery Disease			
Yes	669	24,414	27.40
No	2,398	415,965	5.76

Abbreviations: IR, Incidence Rate; MACE, Major Adverse Cardiac Events, including AMI, stroke or CV death

* Baseline period began July 1, 2003.

[†] IR: Incidence Rate per 1,000 person-years

[§] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	Any MACE Outcome		
	Cases	Person-years[§]	IR[†]
Angina			
Yes	92	3,420	26.90
No	2,975	436,958	6.81
Congestive Heart Failure			
Yes	247	7,427	33.26
No	2,820	432,951	6.51
Atrial Fibrillation			
Yes	152	10,030	15.15
No	2,915	430,349	6.77
Antiarrhythmic Medications			
Yes	1,273	81,456	15.63
No	1,794	358,923	5.00
Hypertension			
Yes	1,739	139,652	12.45
No	1,328	300,727	4.42
Antihypertensives			
Yes	2,191	187,785	11.67
No	876	252,594	3.47
Diabetes			
Yes	646	36,585	17.66
No	2,421	403,794	6.00
High CV Risk Composite			
Yes	2,422	210,731	11.49
No	645	229,648	2.81

Abbreviations: IR, Incidence Rate; MACE, Major Adverse Cardiac Events, including AMI, stroke or CV death

* Baseline period began July 1, 2003.

[†] IR: Incidence Rate per 1,000 person-years

[§] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	Any MACE Outcome		
	Cases	Person-years[§]	IR[†]
Hyperlipidemia			
Yes	1,571	147,949	10.62
No	1,496	292,430	5.12
Ischemic Heart Disease, excluding AMI			
Yes	708	26,770	26.45
No	2,359	413,609	5.70
Acute Myocardial Infarction			
Yes	52	841	61.82
No	3,015	439,537	6.86
Stroke			
Yes	27	2,063	13.09
No	3,040	438,315	6.94
Hypertriglyceridemia			
Yes	23	2,910	7.90
No	3,044	437,469	6.96
Organ Transplant			
Yes	19	1,828	10.39
No	3,048	438,551	6.95
Alcohol Use / Abuse			
Yes	23	1,677	13.71
No	3,044	438,702	6.94
Smoking			
Yes	118	11,423	10.33
No	2,949	428,956	6.87

Abbreviations: IR, Incidence Rate; MACE, Major Adverse Cardiac Events, including AMI, stroke or CV death

* Baseline period began July 1, 2003.

† IR: Incidence Rate per 1,000 person-years

§ Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	Any MACE Outcome		
	Cases	Person-years[§]	IR[†]
Overweight / Obesity			
Yes	131	17,164	7.63
No	2,936	423,215	6.94
Gout			
Yes	50	3,273	15.28
No	3,017	437,106	6.90
Rheumatoid Arthritis			
Yes	71	6,252	11.36
No	2,996	434,127	6.90
Dementia			
Yes	54	1,504	35.91
No	3,013	438,875	6.87
Peptic Ulcer Disease			
Yes	29	1,757	16.50
No	3,038	438,621	6.93
Chronic Obstructive Pulmonary			
Yes	242	10,449	23.16
No	2,825	429,930	6.57
Renal Impairment / Dialysis			
Yes	247	9,593	25.75
No	2,820	430,786	6.55
Open Heart Surgeries			
Yes	59	1,695	34.80
No	3,008	438,683	6.86

Abbreviations: IR, Incidence Rate; MACE, Major Adverse Cardiac Events, including AMI, stroke or CV death

* Baseline period began July 1, 2003.

[†] IR: Incidence Rate per 1,000 person-years

[§] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B1. Incidence of Claims-Identified Cardiovascular Events by Select Baseline* Characteristics, Optum Research Database: 01 January 2004 - 30 September 2012

	Any MACE Outcome		
	Cases	Person-years[§]	IR[†]
Cholesterol Lowering Therapies			
Yes	1,403	123,997	11.31
No	1,664	316,382	5.26
Any CV Drug[‡]			
Yes	2,418	226,744	10.66
No	649	213,634	3.04
Any History of Cancer			
Yes	272	27,965	9.73
No	2,795	412,413	6.78

Abbreviations: CV, Cardiovascular Disease; IR, Incidence Rate; MACE, Major Adverse Cardiac Events, including AMI, stroke or CV death

* Baseline period began July 1, 2003.

[†] IR: Incidence Rate per 1,000 person-years

[‡] CV drugs include antihypertensive medications, cholesterol lowering therapies and antiarrhythmic medications.

[§] Follow-up time for each outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of the outcome, disenrollment from the health plan, death or end of study period.

Table B2. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified Cardiovascular Outcomes, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI	Adjusted IRR‡,‖	95% CI	Crude IRR§	95% CI	Adjusted IRR§,‖	95% CI
AMI											
Overall	1,535	442,646	3.47	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	1,061	319,905	3.32	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	474	122,741	3.86	1.16	1.04 - 1.30	0.95	0.86 - 1.06	----	---- - ----	----	---- - ----
Oxybutynin	134	32,164	4.17	1.26	1.05 - 1.50	1.06	0.89 - 1.27	1.11	0.91 - 1.36	1.16	0.95 - 1.41
Tolterodine	151	34,670	4.36	1.31	1.11 - 1.56	1.02	0.86 - 1.21	1.19	0.98 - 1.44	1.11	0.91 - 1.34
Solifenacin	94	33,000	2.85	0.86	0.70 - 1.06	0.75	0.61 - 0.92	0.67	0.54 - 0.84	0.73	0.59 - 0.92
Darifenacin	57	14,487	3.93	1.19	0.91 - 1.55	0.95	0.73 - 1.25	1.02	0.77 - 1.35	1.00	0.76 - 1.32
Fesoterodine	12	2,812	4.27	1.29	0.73 - 2.27	1.02	0.58 - 1.80	1.11	0.62 - 1.96	1.07	0.60 - 1.89
Trospium	26	5,607	4.64	1.40	0.95 - 2.06	1.00	0.68 - 1.48	1.21	0.82 - 1.80	1.03	0.70 - 1.54
Stroke											
Overall	1,474	442,603	3.33	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	954	319,927	2.98	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	520	122,676	4.24	1.42	1.28 - 1.58	1.15	1.03 - 1.28	----	---- - ----	----	---- - ----
Oxybutynin	128	32,166	3.98	1.33	1.11 - 1.60	1.11	0.92 - 1.34	0.92	0.75 - 1.12	0.96	0.79 - 1.17
Tolterodine	166	34,646	4.79	1.61	1.36 - 1.89	1.22	1.03 - 1.44	1.19	0.99 - 1.43	1.09	0.91 - 1.31
Solifenacin	125	32,963	3.79	1.27	1.06 - 1.53	1.10	0.91 - 1.32	0.86	0.70 - 1.05	0.94	0.77 - 1.15
Darifenacin	67	14,474	4.63	1.55	1.21 - 1.99	1.23	0.96 - 1.58	1.11	0.86 - 1.43	1.09	0.84 - 1.40
Fesoterodine	7	2,822	2.48	0.83	0.40 - 1.75	0.65	0.31 - 1.38	0.58	0.27 - 1.22	0.56	0.27 - 1.19
Trospium	27	5,605	4.82	1.62	1.10 - 2.37	1.20	0.82 - 1.76	1.14	0.78 - 1.69	1.04	0.71 - 1.53

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified Cardiovascular Outcomes, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI	Adjusted IRR‡,‖	95% CI	Crude IRR§	95% CI	Adjusted IRR§,‖	95% CI
CV Death (combined)											
Overall	308	444,948	0.69	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	207	321,754	0.64	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	101	123,193	0.82	1.27	1.00 - 1.62	0.97	0.77 - 1.24	----	---- - ----	----	---- - ----
Oxybutynin	26	32,311	0.80	1.25	0.83 - 1.88	0.99	0.66 - 1.49	0.98	0.62 - 1.52	1.04	0.66 - 1.62
Tolterodine	31	34,776	0.89	1.39	0.95 - 2.02	0.96	0.66 - 1.40	1.13	0.74 - 1.72	0.99	0.65 - 1.52
Solifenacin	26	33,088	0.79	1.22	0.81 - 1.84	1.03	0.69 - 1.55	0.94	0.60 - 1.47	1.10	0.70 - 1.72
Darifenacin	11	14,549	0.76	1.18	0.64 - 2.16	0.88	0.48 - 1.61	0.91	0.49 - 1.71	0.89	0.48 - 1.67
Fesoterodine	4	2,836	1.41	2.19	0.82 - 5.90	1.61	0.60 - 4.33	1.75	0.64 - 4.76	1.69	0.62 - 4.58
Trospium	3	5,633	0.53	0.83	0.26 - 2.59	0.54	0.17 - 1.68	0.64	0.20 - 2.02	0.51	0.16 - 1.60
CHD Death											
Overall	268	444,948	0.60	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	185	321,754	0.57	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	83	123,193	0.67	1.17	0.90 - 1.52	0.89	0.68 - 1.15	----	---- - ----	----	---- - ----
Oxybutynin	20	32,311	0.62	1.08	0.68 - 1.71	0.85	0.53 - 1.35	0.89	0.54 - 1.48	0.95	0.58 - 1.58
Tolterodine	26	34,776	0.75	1.30	0.86 - 1.96	0.89	0.59 - 1.35	1.16	0.73 - 1.84	1.02	0.64 - 1.62
Solifenacin	21	33,088	0.63	1.10	0.70 - 1.73	0.93	0.59 - 1.46	0.92	0.56 - 1.51	1.07	0.65 - 1.76
Darifenacin	10	14,549	0.69	1.20	0.63 - 2.26	0.88	0.47 - 1.67	1.02	0.53 - 1.98	1.00	0.52 - 1.93
Fesoterodine	3	2,836	1.06	1.84	0.59 - 5.76	1.34	0.43 - 4.18	1.59	0.50 - 5.04	1.53	0.48 - 4.85
Trospium	3	5,633	0.53	0.93	0.30 - 2.90	0.59	0.19 - 1.85	0.78	0.25 - 2.48	0.62	0.20 - 1.97

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified Cardiovascular Outcomes, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI	Adjusted IRR‡,‖	95% CI	Crude IRR§	95% CI	Adjusted IRR§,‖	95% CI
Cerebrovascular Death											
Overall	60	444,948	0.13	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	32	321,754	0.10	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	28	123,193	0.23	2.29	1.38 - 3.80	1.87	1.12 - 3.12	----	---- - ----	----	---- - ----
Oxybutynin	7	32,311	0.22	2.18	0.96 - 4.94	1.83	0.81 - 4.16	0.94	0.40 - 2.21	0.98	0.42 - 2.31
Tolterodine	9	34,776	0.26	2.60	1.24 - 5.45	1.92	0.91 - 4.05	1.20	0.54 - 2.66	1.09	0.49 - 2.41
Solifenacin	9	33,088	0.27	2.73	1.31 - 5.73	2.44	1.16 - 5.12	1.29	0.58 - 2.85	1.47	0.66 - 3.25
Darifenacin	2	14,549	0.14	1.38	0.33 - 5.77	1.10	0.26 - 4.61	0.57	0.14 - 2.42	0.56	0.13 - 2.38
Fesoterodine	1	2,836	0.35	3.55	0.48 - 25.95	2.83	0.39 - 20.72	1.57	0.21 - 11.57	1.52	0.21 - 11.20
Trospium	0	5,633	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----
All Cause Mortality											
Overall	1,769	444,948	3.98	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	1,224	321,754	3.80	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	545	123,193	4.42	1.16	1.05 - 1.29	0.95	0.85 - 1.05	----	---- - ----	----	---- - ----
Oxybutynin	162	32,311	5.01	1.32	1.12 - 1.55	1.10	0.94 - 1.30	1.19	0.99 - 1.43	1.24	1.03 - 1.49
Tolterodine	173	34,776	4.97	1.31	1.12 - 1.53	0.99	0.85 - 1.16	1.18	0.99 - 1.42	1.09	0.91 - 1.30
Solifenacin	117	33,088	3.54	0.93	0.77 - 1.12	0.81	0.67 - 0.98	0.74	0.61 - 0.91	0.82	0.67 - 1.01
Darifenacin	55	14,549	3.78	0.99	0.76 - 1.30	0.79	0.60 - 1.03	0.84	0.63 - 1.11	0.82	0.62 - 1.09
Fesoterodine	12	2,836	4.23	1.11	0.63 - 1.96	0.87	0.49 - 1.53	0.96	0.54 - 1.69	0.92	0.52 - 1.63
Trospium	26	5,633	4.62	1.21	0.82 - 1.79	0.85	0.58 - 1.25	1.05	0.71 - 1.55	0.88	0.60 - 1.31

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified Cardiovascular Outcomes, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time					Reference: Rate in the Person-time Exposed to any of the Other Medications				
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI		Adjusted IRR‡,‖	95% CI	Crude IRR§	95% CI		Adjusted IRR§,‖	95% CI
Any MACE Outcome													
Overall	3,067	440,379	6.96	----	----	----	----	---- ----	----	----	----	----	---- ----
Unexposed	2,056	318,145	6.46	Ref	----	----	----	---- ----	----	----	----	----	---- ----
All Drugs	1,011	122,233	8.27	1.28	1.19	1.38	1.03	0.96 1.12	----	----	----	----	---- ----
Oxybutynin	268	32,023	8.37	1.30	1.14	1.47	1.08	0.95 1.23	1.02	0.88	1.17	1.06	0.92 1.22
Tolterodine	324	34,535	9.38	1.45	1.29	1.63	1.10	0.98 1.24	1.20	1.05	1.37	1.10	0.97 1.26
Solifenacin	225	32,877	6.84	1.06	0.92	1.22	0.91	0.80 1.05	0.78	0.67	0.90	0.85	0.73 0.99
Darifenacin	123	14,420	8.53	1.32	1.10	1.58	1.05	0.87 1.26	1.04	0.86	1.25	1.02	0.84 1.23
Fesoterodine	17	2,799	6.07	0.94	0.58	1.52	0.74	0.46 1.19	0.73	0.45	1.18	0.71	0.44 1.14
Trospium	54	5,580	9.68	1.50	1.14	1.96	1.08	0.82 1.41	1.18	0.90	1.55	1.04	0.79 1.36

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2.1. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI	Adjusted IRR‡,	95% CI	Crude IRR§	95% CI	Adjusted IRR§,	95% CI
AMI											
Overall	873	99,244	8.80	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	574	64,045	8.96	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	299	35,199	8.49	0.95	0.82 - 1.09	0.95	0.83 - 1.10	----	---- - ----	----	---- - ----
Oxybutynin	82	8,690	9.44	1.05	0.84 - 1.33	1.06	0.84 - 1.34	1.15	0.89 - 1.49	1.16	0.90 - 1.49
Tolterodine	105	11,089	9.47	1.06	0.86 - 1.30	1.05	0.85 - 1.29	1.18	0.93 - 1.49	1.17	0.92 - 1.48
Solifenacin	56	8,499	6.59	0.74	0.56 - 0.97	0.76	0.57 - 1.00	0.72	0.54 - 0.97	0.75	0.56 - 1.00
Darifenacin	30	4,225	7.10	0.79	0.55 - 1.14	0.79	0.55 - 1.14	0.82	0.56 - 1.19	0.81	0.56 - 1.18
Fesoterodine	8	850	9.41	1.05	0.52 - 2.11	1.06	0.53 - 2.13	1.11	0.55 - 2.24	1.12	0.56 - 2.27
Trospium	18	1,847	9.75	1.09	0.68 - 1.74	1.03	0.65 - 1.65	1.16	0.72 - 1.86	1.06	0.66 - 1.71
Stroke											
Overall	826	99,154	8.33	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	502	63,988	7.85	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	324	35,166	9.21	1.17	1.02 - 1.35	1.16	1.01 - 1.33	----	---- - ----	----	---- - ----
Oxybutynin	79	8,690	9.09	1.16	0.91 - 1.47	1.15	0.91 - 1.46	0.98	0.76 - 1.27	0.99	0.77 - 1.27
Tolterodine	110	11,082	9.93	1.27	1.03 - 1.56	1.23	1.00 - 1.51	1.12	0.89 - 1.41	1.09	0.86 - 1.37
Solifenacin	69	8,484	8.13	1.04	0.81 - 1.33	1.06	0.82 - 1.36	0.85	0.65 - 1.11	0.88	0.68 - 1.15
Darifenacin	47	4,205	11.20	1.42	1.06 - 1.92	1.40	1.04 - 1.89	1.25	0.92 - 1.70	1.25	0.91 - 1.70
Fesoterodine	5	854	5.85	0.75	0.31 - 1.80	0.75	0.31 - 1.80	0.63	0.26 - 1.52	0.64	0.26 - 1.54
Trospium	14	1,850	7.57	0.96	0.57 - 1.64	0.93	0.55 - 1.59	0.81	0.48 - 1.39	0.80	0.47 - 1.36

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2.1. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time					Reference: Rate in the Person-time Exposed to any of the Other Medications				
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI	Adjusted IRR‡,	95% CI		Crude IRR§	95% CI	Adjusted IRR§,	95% CI	
CV Death (combined)													
Overall	228	100,471	2.27	----	---- - ----	----	---- - ----		----	---- - ----	----	---- - ----	
Unexposed	147	64,995	2.26	Ref	---- - ----	----	---- - ----		----	---- - ----	----	---- - ----	
All Drugs	81	35,475	2.28	1.01	0.77 - 1.32	1.01	0.77 - 1.33		----	---- - ----	----	---- - ----	
Oxybutynin	21	8,781	2.39	1.06	0.67 - 1.67	1.06	0.67 - 1.67		1.06	0.65 - 1.75	1.07	0.65 - 1.76	
Tolterodine	27	11,162	2.42	1.07	0.71 - 1.61	1.04	0.69 - 1.57		1.09	0.69 - 1.73	1.07	0.67 - 1.70	
Solifenacin	19	8,546	2.22	0.98	0.61 - 1.59	1.02	0.63 - 1.65		0.97	0.58 - 1.61	1.02	0.61 - 1.71	
Darifenacin	10	4,253	2.35	1.04	0.55 - 1.97	1.03	0.54 - 1.96		1.03	0.53 - 2.00	1.02	0.53 - 1.98	
Fesoterodine	2	865	2.31	1.02	0.25 - 4.13	1.03	0.26 - 4.16		1.01	0.25 - 4.12	1.03	0.25 - 4.21	
Trospium	2	1,867	1.07	0.47	0.12 - 1.91	0.44	0.11 - 1.79		0.46	0.11 - 1.85	0.40	0.10 - 1.61	
CHD Death													
Overall	203	100,471	2.02	----	---- - ----	----	---- - ----		----	---- - ----	----	---- - ----	
Unexposed	135	64,995	2.08	Ref	---- - ----	----	---- - ----		----	---- - ----	----	---- - ----	
All Drugs	68	35,475	1.92	0.92	0.69 - 1.24	0.92	0.69 - 1.24		----	---- - ----	----	---- - ----	
Oxybutynin	15	8,781	1.71	0.82	0.48 - 1.40	0.82	0.48 - 1.40		0.86	0.48 - 1.53	0.87	0.49 - 1.54	
Tolterodine	23	11,162	2.06	0.99	0.64 - 1.54	0.97	0.62 - 1.50		1.11	0.67 - 1.84	1.10	0.66 - 1.81	
Solifenacin	16	8,546	1.87	0.90	0.54 - 1.51	0.94	0.56 - 1.57		0.97	0.55 - 1.70	1.02	0.58 - 1.79	
Darifenacin	10	4,253	2.35	1.13	0.60 - 2.15	1.12	0.59 - 2.14		1.27	0.65 - 2.48	1.25	0.64 - 2.45	
Fesoterodine	2	865	2.31	1.11	0.28 - 4.50	1.12	0.28 - 4.54		1.21	0.30 - 4.95	1.24	0.30 - 5.05	
Trospium	2	1,867	1.07	0.52	0.13 - 2.08	0.48	0.12 - 1.94		0.55	0.13 - 2.23	0.47	0.12 - 1.94	

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2.1. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI	Adjusted IRR‡,	95% CI	Crude IRR§	95% CI	Adjusted IRR§,	95% CI
Cerebrovascular Death											
Overall	37	100,471	0.37	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	18	64,995	0.28	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	19	35,475	0.54	1.93	1.01 - 3.68	1.93	1.01 - 3.68	----	---- - ----	----	---- - ----
Oxybutynin	6	8,781	0.68	2.47	0.98 - 6.22	2.48	0.99 - 6.26	1.40	0.53 - 3.69	1.42	0.54 - 3.73
Tolterodine	7	11,162	0.63	2.26	0.95 - 5.42	2.18	0.91 - 5.22	1.27	0.50 - 3.23	1.23	0.49 - 3.14
Solifenacin	5	8,546	0.59	2.11	0.78 - 5.69	2.18	0.81 - 5.89	1.13	0.41 - 3.12	1.21	0.43 - 3.35
Darifenacin	1	4,253	0.24	0.85	0.11 - 6.36	0.84	0.11 - 6.29	0.41	0.05 - 3.05	0.40	0.05 - 3.02
Fesoterodine	0	865	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	0	1,867	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----
All Cause Mortality											
Overall	1,074	100,471	10.70	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	712	64,995	11.00	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	362	35,475	10.20	0.93	0.82 - 1.06	0.94	0.83 - 1.06	----	---- - ----	----	---- - ----
Oxybutynin	102	8,781	11.60	1.06	0.86 - 1.30	1.07	0.87 - 1.31	1.19	0.95 - 1.50	1.20	0.95 - 1.51
Tolterodine	115	11,162	10.30	0.94	0.77 - 1.15	0.93	0.76 - 1.13	1.01	0.81 - 1.27	1.00	0.80 - 1.25
Solifenacin	79	8,546	9.24	0.84	0.67 - 1.06	0.88	0.70 - 1.11	0.88	0.69 - 1.13	0.92	0.71 - 1.18
Darifenacin	41	4,253	9.64	0.88	0.64 - 1.21	0.88	0.64 - 1.20	0.94	0.68 - 1.30	0.93	0.67 - 1.29
Fesoterodine	7	865	8.09	0.74	0.35 - 1.55	0.75	0.36 - 1.58	0.79	0.37 - 1.67	0.80	0.38 - 1.69
Trospium	18	1,867	9.64	0.88	0.55 - 1.40	0.82	0.51 - 1.31	0.94	0.59 - 1.51	0.86	0.53 - 1.38

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2.1. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time					Reference: Rate in the Person-time Exposed to any of the Other Medications				
	No. of cases	Person-Years*	IR†	Crude IRR‡	95% CI		Adjusted IRR‡,‖	95% CI	Crude IRR§	95% CI		Adjusted IRR§,‖	95% CI
Any MACE Outcome													
Overall	1,762	97,968	18.00	----	----	- ----	----	---- - ----	----	----	- ----	----	---- - ----
Unexposed	1,120	63,071	17.80	Ref	----	- ----	----	---- - ----	----	----	- ----	----	---- - ----
All Drugs	642	34,897	18.40	1.04	0.94	- 1.14	1.03	0.94 - 1.14	----	----	- ----	----	---- - ----
Oxybutynin	166	8,602	19.30	1.09	0.92	- 1.28	1.09	0.92 - 1.28	1.07	0.89	- 1.27	1.07	0.90 - 1.28
Tolterodine	222	11,006	20.20	1.14	0.98	- 1.31	1.12	0.97 - 1.29	1.15	0.98	- 1.35	1.12	0.95 - 1.32
Solifenacin	132	8,438	15.60	0.88	0.74	- 1.06	0.90	0.75 - 1.08	0.81	0.67	- 0.98	0.84	0.70 - 1.02
Darifenacin	77	4,181	18.40	1.04	0.82	- 1.31	1.03	0.82 - 1.30	1.00	0.79	- 1.27	1.00	0.78 - 1.26
Fesoterodine	12	839	14.30	0.81	0.46	- 1.42	0.81	0.46 - 1.43	0.77	0.44	- 1.37	0.78	0.44 - 1.38
Trospium	33	1,831	18.00	1.01	0.72	- 1.43	0.97	0.68 - 1.37	0.98	0.69	- 1.39	0.92	0.65 - 1.31

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

† IR: Incidence Rate per 1,000 person-years

‡ Referent category is unexposed person-time.

§ Referent category is person-time exposed to any other OAB medication.

‖ Adjusted for baseline age group and gender, using Poisson regression analysis

Table B2.2. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients with High Cardiovascular Event Risk*, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years[†]	IR[‡]	Crude IRR[§]	95% CI	Adjusted IRR[§,¶]	95% CI	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
AMI											
Overall	1,241	212,468	5.84	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	836	144,715	5.78	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	405	67,753	5.98	1.03	0.92 - 1.17	0.96	0.85 - 1.08	----	---- - ----	----	---- - ----
Oxybutynin	117	18,044	6.48	1.12	0.93 - 1.36	1.07	0.88 - 1.30	1.12	0.90 - 1.39	1.17	0.94 - 1.45
Tolterodine	128	19,046	6.72	1.16	0.97 - 1.40	1.02	0.85 - 1.23	1.18	0.96 - 1.46	1.11	0.90 - 1.37
Solifenacin	81	17,761	4.56	0.79	0.63 - 0.99	0.76	0.61 - 0.96	0.70	0.55 - 0.90	0.75	0.59 - 0.96
Darifenacin	46	8,077	5.70	0.99	0.73 - 1.33	0.91	0.67 - 1.22	0.95	0.70 - 1.29	0.94	0.69 - 1.28
Fesoterodine	11	1,628	6.76	1.17	0.65 - 2.12	1.07	0.59 - 1.93	1.13	0.62 - 2.06	1.12	0.61 - 2.04
Trospium	22	3,197	6.88	1.19	0.78 - 1.82	0.99	0.65 - 1.51	1.16	0.75 - 1.78	1.01	0.66 - 1.56
Stroke											
Overall	1,123	212,485	5.29	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	715	144,773	4.94	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	408	67,712	6.03	1.22	1.08 - 1.38	1.10	0.98 - 1.25	----	---- - ----	----	---- - ----
Oxybutynin	109	18,039	6.04	1.22	1.00 - 1.50	1.14	0.93 - 1.39	1.00	0.81 - 1.25	1.04	0.84 - 1.30
Tolterodine	124	19,034	6.51	1.32	1.09 - 1.60	1.13	0.93 - 1.37	1.12	0.90 - 1.38	1.03	0.83 - 1.27
Solifenacin	93	17,737	5.24	1.06	0.86 - 1.32	1.01	0.82 - 1.26	0.83	0.66 - 1.05	0.89	0.71 - 1.12
Darifenacin	54	8,067	6.69	1.36	1.03 - 1.79	1.22	0.93 - 1.61	1.13	0.85 - 1.50	1.13	0.85 - 1.50
Fesoterodine	6	1,634	3.67	0.74	0.33 - 1.66	0.67	0.30 - 1.50	0.60	0.27 - 1.35	0.60	0.27 - 1.35
Trospium	22	3,201	6.87	1.39	0.91 - 2.13	1.18	0.77 - 1.81	1.15	0.75 - 1.76	1.07	0.70 - 1.64

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Patients with a high risk for cardiovascular events will be defined as having one or more of the following conditions identified by claims in the baseline period: Cerebrovascular disease, coronary artery disease, angina, acute myocardial infarction, heart failure, arrhythmia (separately for diagnosis and medications), hypertension (separately for diagnosis and medications), hyperlipidemia (separately for diagnosis and medications), diabetes

[†] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

[‡] IR: Incidence Rate per 1,000 person-years

[§] Referent category is unexposed person-time.

[‖] Referent category is person-time exposed to another OAB medication.

[¶] Adjusted for baseline age group and gender,using Poisson regression analysis

Table B2.2. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients with High Cardiovascular Event Risk*, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years[†]	IR[‡]	Crude IRR[§]	95% CI	Adjusted IRR[§,¶]	95% CI	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
CV Death (combined)											
Overall	272	214,275	1.27	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	184	146,146	1.26	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	88	68,129	1.29	1.03	0.80 - 1.32	0.92	0.71 - 1.19	----	---- - ----	----	---- - ----
Oxybutynin	23	18,166	1.27	1.01	0.65 - 1.55	0.93	0.61 - 1.44	0.97	0.60 - 1.57	1.04	0.65 - 1.67
Tolterodine	27	19,136	1.41	1.12	0.75 - 1.68	0.92	0.62 - 1.39	1.13	0.72 - 1.78	1.01	0.64 - 1.59
Solifenacin	22	17,837	1.23	0.98	0.63 - 1.52	0.95	0.61 - 1.48	0.94	0.58 - 1.52	1.06	0.65 - 1.71
Darifenacin	10	8,124	1.23	0.98	0.52 - 1.85	0.87	0.46 - 1.65	0.95	0.49 - 1.83	0.95	0.49 - 1.83
Fesoterodine	4	1,646	2.43	1.93	0.72 - 5.20	1.71	0.63 - 4.59	1.92	0.71 - 5.24	1.90	0.70 - 5.18
Trospium	2	3,221	0.62	0.49	0.12 - 1.99	0.38	0.10 - 1.55	0.47	0.12 - 1.90	0.38	0.09 - 1.54
CHD Death											
Overall	243	214,275	1.13	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	168	146,146	1.15	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	75	68,129	1.10	0.96	0.73 - 1.26	0.85	0.65 - 1.12	----	---- - ----	----	---- - ----
Oxybutynin	18	18,166	0.99	0.86	0.53 - 1.40	0.80	0.49 - 1.29	0.87	0.51 - 1.48	0.93	0.55 - 1.58
Tolterodine	24	19,136	1.25	1.09	0.71 - 1.67	0.89	0.58 - 1.37	1.20	0.74 - 1.96	1.07	0.66 - 1.74
Solifenacin	19	17,837	1.07	0.93	0.58 - 1.49	0.89	0.55 - 1.43	0.96	0.57 - 1.61	1.08	0.64 - 1.82
Darifenacin	9	8,124	1.11	0.96	0.49 - 1.88	0.85	0.44 - 1.67	1.01	0.50 - 2.02	1.01	0.50 - 2.02
Fesoterodine	3	1,646	1.82	1.59	0.51 - 4.97	1.39	0.44 - 4.34	1.68	0.53 - 5.34	1.66	0.52 - 5.27
Trospium	2	3,221	0.62	0.54	0.13 - 2.18	0.42	0.10 - 1.68	0.55	0.14 - 2.25	0.45	0.11 - 1.83

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Patients with a high risk for cardiovascular events will be defined as having one or more of the following conditions identified by claims in the baseline period: Cerebrovascular disease, coronary artery disease, angina, acute myocardial infarction, heart failure, arrhythmia (separately for diagnosis and medications), hypertension (separately for diagnosis and medications), hyperlipidemia (separately for diagnosis and medications), diabetes

[†] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

[‡] IR: Incidence Rate per 1,000 person-years

[§] Referent category is unexposed person-time.

[‖] Referent category is person-time exposed to another OAB medication.

[¶] Adjusted for baseline age group and gender,using Poisson regression analysis

Table B2.2. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients with High Cardiovascular Event Risk*, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years[†]	IR[‡]	Crude IRR[§]	95% CI	Adjusted IRR[§,¶]	95% CI	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Cerebrovascular Death											
Overall	48	214,275	0.22	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	26	146,146	0.18	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	22	68,129	0.32	1.82	1.03 - 3.20	1.74	0.98 - 3.08	----	---- - ----	----	---- - ----
Oxybutynin	6	18,166	0.33	1.86	0.76 - 4.51	1.83	0.75 - 4.47	1.03	0.40 - 2.64	1.08	0.42 - 2.77
Tolterodine	7	19,136	0.37	2.06	0.89 - 4.74	1.85	0.80 - 4.29	1.19	0.49 - 2.93	1.10	0.45 - 2.71
Solifenacin	6	17,837	0.34	1.89	0.78 - 4.59	1.94	0.80 - 4.72	1.06	0.41 - 2.70	1.16	0.45 - 2.96
Darifenacin	2	8,124	0.25	1.38	0.33 - 5.83	1.34	0.32 - 5.66	0.74	0.17 - 3.16	0.74	0.17 - 3.17
Fesoterodine	1	1,646	0.61	3.42	0.46 - 25.17	3.30	0.45 - 24.37	1.92	0.26 - 14.30	1.90	0.26 - 14.12
Trospium	0	3,221	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----	0.00	0.00 - ----
All Cause Mortality											
Overall	1,427	214,275	6.66	----	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
Unexposed	970	146,146	6.64	Ref	---- - ----	----	---- - ----	----	---- - ----	----	---- - ----
All Drugs	457	68,129	6.71	1.01	0.90 - 1.13	0.93	0.83 - 1.04	----	---- - ----	----	---- - ----
Oxybutynin	135	18,166	7.43	1.12	0.94 - 1.34	1.06	0.89 - 1.27	1.15	0.94 - 1.41	1.20	0.98 - 1.47
Tolterodine	150	19,136	7.84	1.18	0.99 - 1.40	1.02	0.86 - 1.21	1.25	1.03 - 1.52	1.16	0.95 - 1.41
Solifenacin	94	17,837	5.27	0.79	0.64 - 0.98	0.77	0.62 - 0.95	0.73	0.58 - 0.92	0.79	0.63 - 0.99
Darifenacin	44	8,124	5.42	0.82	0.60 - 1.10	0.75	0.55 - 1.01	0.79	0.58 - 1.07	0.79	0.58 - 1.07
Fesoterodine	11	1,646	6.68	1.01	0.56 - 1.82	0.91	0.50 - 1.65	1.00	0.55 - 1.81	0.98	0.54 - 1.79
Trospium	23	3,221	7.14	1.08	0.71 - 1.63	0.87	0.58 - 1.32	1.07	0.70 - 1.62	0.93	0.61 - 1.41

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Patients with a high risk for cardiovascular events will be defined as having one or more of the following conditions identified by claims in the baseline period: Cerebrovascular disease, coronary artery disease, angina, acute myocardial infarction, heart failure, arrhythmia (separately for diagnosis and medications), hypertension (separately for diagnosis and medications), hyperlipidemia (separately for diagnosis and medications), diabetes

[†] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

[‡] IR: Incidence Rate per 1,000 person-years

[§] Referent category is unexposed person-time.

[‖] Referent category is person-time exposed to another OAB medication.

[¶] Adjusted for baseline age group and gender,using Poisson regression analysis

Table B2.2. Crude and Adjusted Association between Antimuscarinic drugs and Claims-Identified Cardiovascular Outcomes, Among Patients with High Cardiovascular Event Risk*, Optum Research Database: 01 January 2004 - 30 September 2012

				Reference: Rate in the Unexposed Person-time				Reference: Rate in the Person-time Exposed to any of the Other Medications			
	No. of cases	Person-Years[†]	IR[‡]	Crude IRR[§]	95% CI	Adjusted IRR[§,¶]	95% CI	Crude IRR	95% CI	Adjusted IRR[¶]	95% CI
Any MACE Outcome											
Overall	2,422	210,731	11.50	**----**	**---- - ----**	**----**	**---- - ----**	----	---- - ----	----	---- - ----
Unexposed	1,592	143,389	11.10	Ref	---- - **----**	----	---- - **----**	----	---- - ----	----	---- - ----
All Drugs	830	67,342	12.30	1.11	1.02 - 1.21	1.01	0.93 - 1.10	----	---- - ----	----	---- - ----
Oxybutynin	232	17,920	12.90	1.17	1.02 - 1.34	1.10	0.96 - 1.26	1.07	0.92 - 1.25	1.12	0.96 - 1.30
Tolterodine	259	18,939	13.70	1.23	1.08 - 1.40	1.06	0.93 - 1.21	1.16	1.00 - 1.34	1.07	0.93 - 1.24
Solifenacin	180	17,663	10.20	0.92	0.79 - 1.07	0.88	0.76 - 1.03	0.78	0.66 - 0.92	0.83	0.71 - 0.98
Darifenacin	100	8,025	12.50	1.12	0.92 - 1.37	1.02	0.83 - 1.25	1.01	0.82 - 1.25	1.01	0.82 - 1.24
Fesoterodine	15	1,617	9.28	0.84	0.50 - 1.39	0.76	0.46 - 1.26	0.75	0.45 - 1.25	0.74	0.45 - 1.24
Trospium	44	3,178	13.80	1.25	0.92 - 1.68	1.04	0.77 - 1.40	1.13	0.83 - 1.53	1.01	0.75 - 1.37

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; IR, Incidence Rate; IRR, Incidence Rate Ratio; MACE, Major Adverse Cardiac Events (AMI, stroke or CV death); Ref, Referent Category

* Patients with a high risk for cardiovascular events will be defined as having one or more of the following conditions identified by claims in the baseline period: Cerebrovascular disease, coronary artery disease, angina, acute myocardial infarction, heart failure, arrhythmia (separately for diagnosis and medications), hypertension (separately for diagnosis and medications), hyperlipidemia (separately for diagnosis and medications), diabetes

[†] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up for each drug exposure ends on the earliest of the following: end of patient use (based on dispensing amount plus 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period. Follow-up time for a particular outcome ends at the first occurrence of that outcome.

[‡] IR: Incidence Rate per 1,000 person-years

[§] Referent category is unexposed person-time.

[ll] Referent category is person-time exposed to another OAB medication.

[¶] Adjusted for baseline age group and gender,using Poisson regression analysis

Table C1a. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 6-month Baseline*, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 46,539)			Women (N = 145,138)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Any of 10 Cancers	2,408	94,181	25.57	2,204	313,863	7.02
< 6 months	1,473	20,430	72.10	787	64,816	12.10
6 months to <1 year	357	16,121	22.10	312	52,527	5.94
1 to < 2 years	265	23,099	11.50	409	76,710	5.33
≥ 2 years	313	34,531	9.06	696	119,810	5.81
Bladder						
< 6 months	380	20,670	18.40	146	64,949	2.25
6 months to <1 year	46	16,653	2.76	14	52,869	0.26
1 to < 2 years	37	24,043	1.54	20	77,484	0.26
≥ 2 years	35	36,455	0.96	20	122,260	0.16
Breast (Women only)						
< 6 months	----	----	----	366	64,916	5.64
6 months to <1 year	----	----	----	180	52,721	3.41
1 to < 2 years	----	----	----	221	77,098	2.87
≥ 2 years	----	----	----	377	120,873	3.12
Colon/Rectum						
< 6 months	43	20,766	2.07	57	64,977	0.88
6 months to <1 year	13	16,787	0.77	24	52,896	0.45
1 to < 2 years	22	24,247	0.91	44	77,495	0.57
≥ 2 years	33	36,773	0.90	56	122,217	0.46
Kidney/Renal Pelvis						
< 6 months	43	20,765	2.07	41	64,980	0.63
6 months to <1 year	15	16,785	0.89	13	52,908	0.25
1 to < 2 years	10	24,250	0.41	10	77,531	0.13
≥ 2 years	18	36,768	0.49	20	122,336	0.16
Lung/Bronchus						
< 6 months	43	20,767	2.07	56	64,978	0.86
6 months to <1 year	19	16,789	1.13	25	52,901	0.47
1 to < 2 years	27	24,256	1.11	53	77,508	0.68
≥ 2 years	39	36,794	1.06	89	122,266	0.73

* Includes only patients who do not meet the definition for baseline cancer in baseline period. Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C1a. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 6-month Baseline*, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 46,539)			Women (N = 145,138)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Melanoma						
< 6 months	5	20,775	0.24	14	64,986	0.22
6 months to <1 year	6	16,802	0.36	11	52,917	0.21
1 to < 2 years	6	24,272	0.25	10	77,545	0.13
≥ 2 years	21	36,823	0.57	24	122,320	0.20
Non-hodgkin's Lymphoma						
< 6 months	43	20,765	2.07	64	64,977	0.98
6 months to <1 year	15	16,785	0.89	23	52,896	0.43
1 to < 2 years	11	24,241	0.45	26	77,501	0.34
≥ 2 years	32	36,754	0.87	50	122,214	0.41
Pancreas						
< 6 months	8	20,774	0.39	13	64,987	0.20
6 months to <1 year	2	16,802	0.12	7	52,920	0.13
1 to < 2 years	11	24,277	0.45	4	77,560	0.05
≥ 2 years	11	36,831	0.30	29	122,400	0.24
Prostate (Men only)						
< 6 months	916	20,577	44.50	----	----	----
6 months to <1 year	243	16,352	14.90	----	----	----
1 to < 2 years	142	23,495	6.04	----	----	----
≥ 2 years	127	35,345	3.59	----	----	----
Uterus (Women only)						
< 6 months	----	----	----	35	64,981	0.54
6 months to <1 year	----	----	----	16	52,911	0.30
1 to < 2 years	----	----	----	25	77,529	0.32
≥ 2 years	----	----	----	32	122,326	0.26

* Includes only patients who do not meet the definition for baseline cancer and do not have V10 (history of cancer) in baseline period. Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C1a.1. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 6-month Baseline* Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 13,795)			Women (N = 24,854)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Any of 10 Cancers	1,133	28,304	40.03	790	57,728	13.68
< 6 months	651	6,060	107.00	307	11,253	27.30
6 months to <1 year	180	4,804	37.50	115	9,357	12.30
1 to < 2 years	135	6,968	19.40	144	14,116	10.20
≥ 2 years	167	10,472	15.90	224	23,002	9.74
Bladder						
< 6 months	131	6,173	21.20	64	11,303	5.66
6 months to <1 year	28	5,054	5.54	7	9,485	0.74
1 to < 2 years	20	7,429	2.69	12	14,398	0.83
≥ 2 years	21	11,495	1.83	13	23,814	0.55
Breast (Women only)						
< 6 months	----	----	----	133	11,295	11.80
6 months to <1 year	----	----	----	53	9,438	5.62
1 to < 2 years	----	----	----	57	14,280	3.99
≥ 2 years	----	----	----	91	23,453	3.88
Colon/Rectum						
< 6 months	16	6,204	2.58	27	11,317	2.39
6 months to <1 year	7	5,104	1.37	14	9,494	1.47
1 to < 2 years	11	7,508	1.47	23	14,395	1.60
≥ 2 years	22	11,632	1.89	23	23,797	0.97
Kidney/Renal Pelvis						
< 6 months	14	6,205	2.26	17	11,318	1.50
6 months to <1 year	8	5,105	1.57	3	9,501	0.32
1 to < 2 years	2	7,512	0.27	3	14,416	0.21
≥ 2 years	10	11,630	0.86	8	23,858	0.34
Lung/Bronchus						
< 6 months	31	6,201	5.00	28	11,316	2.47
6 months to <1 year	13	5,101	2.55	11	9,496	1.16
1 to < 2 years	17	7,506	2.26	26	14,403	1.81
≥ 2 years	26	11,633	2.24	37	23,826	1.55

* Includes only patients who do not meet the definition for baseline cancer in baseline period. Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C1a.1. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 6-month Baseline* Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 13,795)			Women (N = 24,854)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Melanoma						
< 6 months	5	6,207	0.81	1	11,322	0.09
6 months to <1 year	2	5,110	0.39	5	9,506	0.53
1 to < 2 years	5	7,519	0.66	3	14,425	0.21
≥ 2 years	8	11,663	0.69	7	23,868	0.29
Non-hodgkin's Lymphoma						
< 6 months	18	6,204	2.90	24	11,317	2.12
6 months to <1 year	7	5,104	1.37	13	9,495	1.37
1 to < 2 years	5	7,506	0.67	10	14,402	0.69
≥ 2 years	17	11,619	1.46	17	23,799	0.71
Pancreas						
< 6 months	4	6,207	0.64	5	11,321	0.44
6 months to <1 year	2	5,111	0.39	5	9,505	0.53
1 to < 2 years	6	7,522	0.80	1	14,427	0.07
≥ 2 years	3	11,661	0.26	16	23,878	0.67
Prostate (Men only)						
< 6 months	436	6,113	71.30	----	----	----
6 months to <1 year	115	4,898	23.50	----	----	----
1 to < 2 years	70	7,144	9.80	----	----	----
≥ 2 years	62	10,868	5.71	----	----	----
Uterus (Women only)						
< 6 months	----	----	----	11	11,319	0.97
6 months to <1 year	----	----	----	5	9,503	0.53
1 to < 2 years	----	----	----	10	14,415	0.69
≥ 2 years	----	----	----	12	23,858	0.50

* Includes only patients who do not meet the definition for baseline cancer and do not have V10 (history of cancer) in baseline period. Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C1b. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 12-month Baseline*, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 45,556)			Women (N = 143,435)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Any of 10 Cancers	2,299	92,408	24.88	2,088	310,322	6.73
< 6 months	1,426	19,997	71.30	726	64,053	11.30
6 months to <1 year	318	15,796	20.10	293	51,925	5.64
1 to < 2 years	251	22,664	11.10	390	75,812	5.14
≥ 2 years	304	33,951	8.95	679	118,532	5.73
Bladder						
< 6 months	368	20,228	18.20	145	64,177	2.26
6 months to <1 year	45	16,305	2.76	15	52,232	0.29
1 to < 2 years	34	23,553	1.44	19	76,528	0.25
≥ 2 years	35	35,783	0.98	20	120,879	0.17
Breast (Women only)						
< 6 months	----	----	----	312	64,152	4.86
6 months to <1 year	----	----	----	168	52,113	3.22
1 to < 2 years	----	----	----	209	76,189	2.74
≥ 2 years	----	----	----	369	119,578	3.09
Colon/Rectum						
< 6 months	41	20,321	2.02	51	64,206	0.79
6 months to <1 year	12	16,434	0.73	23	52,261	0.44
1 to < 2 years	21	23,751	0.88	42	76,544	0.55
≥ 2 years	31	36,095	0.86	56	120,842	0.46
Kidney/Renal Pelvis						
< 6 months	43	20,321	2.12	40	64,208	0.62
6 months to <1 year	12	16,432	0.73	10	52,272	0.19
1 to < 2 years	10	23,752	0.42	10	76,579	0.13
≥ 2 years	16	36,100	0.44	20	120,963	0.17
Lung/Bronchus						
< 6 months	37	20,323	1.82	54	64,208	0.84
6 months to <1 year	16	16,436	0.97	26	52,265	0.50
1 to < 2 years	26	23,759	1.09	51	76,553	0.67
≥ 2 years	37	36,120	1.02	88	120,893	0.73

* Includes only patients who do not meet the definition for baseline cancer and do not have V10 (history of cancer) in baseline period. Baseline period began January 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C1b. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 12-month Baseline*, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 45,556)			Women (N = 143,435)		
	Cases	Person-years[†]	IR[‡]	Cases	Person-years[†]	IR[‡]
Melanoma						
< 6 months	4	20,331	0.20	13	64,215	0.20
6 months to <1 year	6	16,448	0.36	9	52,281	0.17
1 to < 2 years	7	23,774	0.29	9	76,592	0.12
≥ 2 years	21	36,143	0.58	22	120,948	0.18
Non-hodgkin's Lymphoma						
< 6 months	42	20,321	2.07	67	64,204	1.04
6 months to <1 year	12	16,432	0.73	20	52,259	0.38
1 to < 2 years	11	23,745	0.46	24	76,548	0.31
≥ 2 years	33	36,074	0.91	48	120,846	0.40
Pancreas						
< 6 months	7	20,329	0.34	13	64,215	0.20
6 months to <1 year	2	16,448	0.12	7	52,283	0.13
1 to < 2 years	10	23,778	0.42	4	76,604	0.05
≥ 2 years	11	36,152	0.30	25	121,027	0.21
Prostate (Men only)						
< 6 months	891	20,138	44.20	----	----	----
6 months to <1 year	215	16,016	13.40	----	----	----
1 to < 2 years	133	23,038	5.77	----	----	----
≥ 2 years	123	34,740	3.54	----	----	----
Uterus (Women only)						
< 6 months	----	----	----	37	64,209	0.58
6 months to <1 year	----	----	----	16	52,273	0.31
1 to < 2 years	----	----	----	24	76,573	0.31
≥ 2 years	----	----	----	32	120,950	0.26

* Includes only patients who do not meet the definition for baseline cancer
Baseline period began January 1, 2003.

[†] Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

[‡] IR: Incidence Rate per 1,000 person-years

Table C1b.1. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 12-month Baseline* Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 13,209)			Women (N = 24,172)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Any of 10 Cancers	1,052	27,282	38.56	734	56,237	13.05
< 6 months	607	5,809	104.00	285	10,941	26.00
6 months to <1 year	161	4,618	34.90	103	9,104	11.30
1 to < 2 years	125	6,719	18.60	133	13,735	9.68
≥ 2 years	159	10,136	15.70	213	22,457	9.48
Bladder						
< 6 months	124	5,911	21.00	63	10,988	5.73
6 months to <1 year	29	4,850	5.98	8	9,217	0.87
1 to < 2 years	18	7,139	2.52	12	13,986	0.86
≥ 2 years	21	11,071	1.90	13	23,213	0.56
Breast (Women only)						
< 6 months	----	----	----	118	10,983	10.70
6 months to <1 year	----	----	----	44	9,182	4.79
1 to < 2 years	----	----	----	52	13,894	3.74
≥ 2 years	----	----	----	89	22,896	3.89
Colon/Rectum						
< 6 months	18	5,940	3.03	22	11,003	2.00
6 months to <1 year	6	4,898	1.23	13	9,228	1.41
1 to < 2 years	10	7,217	1.39	21	13,986	1.50
≥ 2 years	20	11,208	1.78	23	23,199	0.99
Kidney/Renal Pelvis						
< 6 months	16	5,941	2.69	15	11,003	1.36
6 months to <1 year	6	4,899	1.22	2	9,234	0.22
1 to < 2 years	2	7,220	0.28	3	14,007	0.21
≥ 2 years	8	11,216	0.71	8	23,262	0.34
Lung/Bronchus						
< 6 months	25	5,939	4.21	25	11,002	2.27
6 months to <1 year	11	4,897	2.25	12	9,229	1.30
1 to < 2 years	16	7,216	2.22	25	13,992	1.79
≥ 2 years	24	11,213	2.14	36	23,229	1.55

* Includes only patients who do not meet the definition for baseline cancer and do not have V10 (history
Baseline period began January 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C1b.1. Incidence of Claims-Identified First Cancer Outcomes by Time since Index Drug Use (Cohort Entry), Based on 12-month Baseline* Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Men (N = 13,209)			Women (N = 24,172)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Melanoma						
< 6 months	4	5,944	0.67	1	11,007	0.09
6 months to <1 year	2	4,904	0.41	4	9,239	0.43
1 to < 2 years	6	7,227	0.83	2	14,016	0.14
≥ 2 years	8	11,237	0.71	5	23,275	0.21
Non-hodgkin's Lymphoma						
< 6 months	16	5,941	2.69	28	11,001	2.55
6 months to <1 year	5	4,900	1.02	11	9,227	1.19
1 to < 2 years	5	7,218	0.69	9	13,992	0.64
≥ 2 years	18	11,198	1.61	15	23,209	0.65
Pancreas						
< 6 months	3	5,944	0.50	5	11,005	0.45
6 months to <1 year	2	4,905	0.41	5	9,238	0.54
1 to < 2 years	6	7,229	0.83	1	14,016	0.07
≥ 2 years	3	11,236	0.27	12	23,285	0.52
Prostate (Men only)						
< 6 months	404	5,858	69.00	----	----	----
6 months to <1 year	102	4,709	21.70	----	----	----
1 to < 2 years	63	6,886	9.15	----	----	----
≥ 2 years	59	10,511	5.61	----	----	----
Uterus (Women only)						
< 6 months	----	----	----	11	11,004	1.00
6 months to <1 year	----	----	----	5	9,236	0.54
1 to < 2 years	----	----	----	9	14,005	0.64
≥ 2 years	----	----	----	12	23,261	0.52

* Includes only patients who do not meet the definition for baseline cancer and do not have V10 (history
Baseline period began January 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Bladder			Breast (Women only)			Colon/Rectum		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	698	414,872	1.68	1,144	315,222	3.63	292	415,647	0.70
Age									
18-44	24	93,115	0.26	89	75,060	1.19	11	93,148	0.12
45-54	105	112,524	0.93	270	92,690	2.91	56	112,622	0.50
55-64	273	120,182	2.27	451	89,071	5.06	82	120,527	0.68
65-74	137	44,304	3.09	166	28,554	5.81	57	44,488	1.28
75+	159	44,746	3.55	168	29,846	5.63	86	44,862	1.92
Gender									
Female	200	317,176	0.63	1,144	315,222	3.63	181	317,198	0.57
Male	498	97,696	5.10	----	----	----	111	98,449	1.13
Alcohol Abuse									
Yes	6	1,512	3.97	2	914	2.19	0	1,524	0.00
No	692	413,360	1.67	1,142	314,308	3.63	292	414,123	0.71
Smoking									
Yes	64	9,621	6.65	22	6,913	3.18	3	9,713	0.31
No	634	405,251	1.56	1,122	308,309	3.64	289	405,934	0.71
Overweight / Obesity									
Yes	17	16,287	1.04	48	13,103	3.66	15	16,275	0.92
No	681	398,585	1.71	1,096	302,119	3.63	277	399,372	0.69
Chronic Obstructive Pulmonary Disease									
Yes	53	9,478	5.59	30	6,329	4.74	14	9,546	1.47
No	645	405,395	1.59	1,114	308,893	3.61	278	406,102	0.68
Renal Impairment / Dialysis									
Yes	45	8,441	5.33	15	4,641	3.23	19	8,485	2.24
No	653	406,431	1.61	1,129	310,580	3.64	273	407,162	0.67

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

	Bladder			Breast (Women only)			Colon/Rectum		
Baseline Patient Characteristics	**Cases**	**Person-years†**	**IR‡**	**Cases**	**Person-years†**	**IR‡**	**Cases**	**Person-years†**	**IR‡**
Diabetes									
Yes	92	34,421	2.67	115	22,823	5.04	43	34,507	1.25
No	606	380,451	1.59	1,029	292,398	3.52	249	381,140	0.65
Endometrial Polyps (Women only)									
Yes	0	536	0.00	4	529	7.56	0	536	0.00
No	200	316,640	0.63	1,140	314,692	3.62	292	316,662	0.92
Irritable Bowel Syndrome									
Yes	4	7,924	0.50	15	6,960	2.16	5	7,921	0.63
No	694	406,948	1.71	1,129	308,261	3.66	287	407,727	0.70
Polycystic Ovary Syndrome (Women only)									
Yes	0	799	0.00	0	799	0.00	0	799	0.00
No	200	316,377	0.63	1,144	314,423	3.64	292	316,399	0.92
Any Cancer Drug									
Yes	19	17,166	1.11	179	15,015	11.92	19	17,177	1.11
No	679	397,706	1.71	965	300,207	3.21	273	398,470	0.69
Alkylating Agents									
Yes	0	141	0.00	0	85	0.00	1	141	7.12
No	698	414,731	1.68	1,144	315,136	3.63	291	415,507	0.70
Antimetabolites									
Yes	8	4,512	1.77	23	3,569	6.44	7	4,513	1.55
No	690	410,360	1.68	1,121	311,653	3.60	285	411,134	0.69

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

	Bladder			Breast (Women only)			Colon/Rectum		
Baseline Patient Characteristics	**Cases**	**Person-years†**	**IR‡**	**Cases**	**Person-years†**	**IR‡**	**Cases**	**Person-years†**	**IR‡**
Antimicrotubule Agents									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	698	414,872	1.68	1,144	315,222	3.63	292	415,647	0.70
Topoisomerase-active Agents									
Yes	0	4	0.00	0	4	0.00	0	4	0.00
No	698	414,868	1.68	1,144	315,218	3.63	292	415,643	0.70
Antineoplastic Antibiotics									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	698	414,872	1.68	1,144	315,222	3.63	292	415,647	0.70
Endocrine Agents									
Yes	9	12,479	0.72	159	11,390	13.96	11	12,486	0.88
No	689	402,393	1.71	985	303,831	3.24	281	403,161	0.70
Biologically-directed Therapies									
Yes	0	133	0.00	1	73	13.76	0	133	0.00
No	698	414,739	1.68	1,143	315,149	3.63	292	415,514	0.70
Immune Therapies									
Yes	2	94	21.18	1	56	17.73	0	98	0.00
No	696	414,778	1.68	1,143	315,165	3.63	292	415,549	0.70
Miscellaneous Agents									
Yes	0	13	0.00	0	10	0.00	0	13	0.00
No	698	414,859	1.68	1,144	315,211	3.63	292	415,634	0.70

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Kidney/Renal Pelvis			Lung/Bronchus			Melanoma		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	170	415,812	0.41	351	415,748	0.84	97	415,931	0.23
Age									
18-44	8	93,154	0.09	5	93,166	0.05	11	93,144	0.12
45-54	31	112,685	0.28	38	112,693	0.34	16	112,686	0.14
55-64	66	120,530	0.55	119	120,510	0.99	34	120,583	0.28
65-74	38	44,503	0.85	97	44,483	2.18	14	44,553	0.31
75+	27	44,940	0.60	92	44,896	2.05	22	44,965	0.49
Gender									
Female	84	317,368	0.26	223	317,267	0.70	59	317,383	0.19
Male	86	98,444	0.87	128	98,481	1.30	38	98,548	0.39
Alcohol Use / Abuse									
Yes	4	1,521	2.63	6	1,517	3.96	0	1,524	0.00
No	166	414,291	0.40	345	414,231	0.83	97	414,407	0.23
Smoking									
Yes	11	9,707	1.13	25	9,688	2.58	1	9,715	0.10
No	159	406,105	0.39	326	406,060	0.80	96	406,216	0.24
Overweight / Obesity									
Yes	8	16,288	0.49	13	16,284	0.80	2	16,298	0.12
No	162	399,524	0.41	338	399,464	0.85	95	399,633	0.24
Chronic Obstructive Pulmonary Disease									
Yes	6	9,550	0.63	53	9,513	5.57	3	9,556	0.31
No	164	406,262	0.40	298	406,235	0.73	94	406,375	0.23
Renal Impairment / Dialysis									
Yes	20	8,475	2.36	14	8,489	1.65	3	8,497	0.35
No	150	407,337	0.37	337	407,259	0.83	94	407,433	0.23

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Kidney/Renal Pelvis			Lung/Bronchus			Melanoma		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Diabetes									
Yes	35	34,507	1.01	43	34,520	1.25	11	34,540	0.32
No	135	381,304	0.35	308	381,228	0.81	86	381,391	0.23
Endometrial Polyps (Women only)									
Yes	0	536	0.00	0	536	0.00	0	536	0.00
No	84	316,832	0.27	223	316,731	0.70	59	316,847	0.19
Irritable Bowel Syndrome									
Yes	2	7,925	0.25	5	7,922	0.63	0	7,929	0.00
No	168	407,887	0.41	346	407,826	0.85	97	408,002	0.24
Polycystic Ovary Syndrome (Women only)									
Yes	0	799	0.00	0	799	0.00	0	799	0.00
No	84	316,569	0.27	223	316,468	0.70	59	316,584	0.19
Any Cancer Drug									
Yes	11	17,177	0.64	26	17,185	1.51	3	17,203	0.17
No	159	398,635	0.40	325	398,563	0.82	94	398,728	0.24
Alkylating Agents									
Yes	0	141	0.00	2	140	14.26	1	141	7.11
No	170	415,671	0.41	349	415,608	0.84	96	415,790	0.23
Antimetabolites									
Yes	5	4,509	1.11	5	4,516	1.11	1	4,520	0.22
No	165	411,303	0.40	346	411,232	0.84	96	411,411	0.23

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Kidney/Renal Pelvis			Lung/Bronchus			Melanoma		
	Cases	Person-years[†]	IR[‡]	Cases	Person-years[†]	IR[‡]	Cases	Person-years[†]	IR[‡]
Antimicrotubule Agents									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	170	415,812	0.41	351	415,748	0.84	97	415,931	0.23
Topoisomerase-active Agents									
Yes	0	4	0.00	0	4	0.00	0	4	0.00
No	170	415,808	0.41	351	415,744	0.84	97	415,926	0.23
Antineoplastic Antibiotics									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	170	415,812	0.41	351	415,748	0.84	97	415,931	0.23
Endocrine Agents									
Yes	6	12,490	0.48	17	12,492	1.36	1	12,505	0.08
No	164	403,322	0.41	334	403,256	0.83	96	403,425	0.24
Biologically-directed Therapies									
Yes	0	133	0.00	3	131	22.90	0	133	0.00
No	170	415,679	0.41	348	415,617	0.84	97	415,798	0.23
Immune Therapies									
Yes	0	98	0.00	0	98	0.00	0	98	0.00
No	170	415,714	0.41	351	415,650	0.84	97	415,833	0.23
Miscellaneous Agents									
Yes	0	13	0.00	0	13	0.00	0	13	0.00
No	170	415,799	0.41	351	415,735	0.84	97	415,918	0.23

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

[†] Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

[‡] IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Non-hodgkin's Lymphoma			Pancreas			Prostate (Men only)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	264	415,622	0.64	85	416,040	0.20	1,428	95,647	14.93
Age									
18-44	18	93,128	0.19	2	93,165	0.02	10	17,891	0.56
45-54	36	112,654	0.32	12	112,722	0.11	136	19,149	7.10
55-64	99	120,494	0.82	29	120,624	0.24	599	29,621	20.22
65-74	53	44,462	1.19	23	44,544	0.52	368	14,916	24.67
75+	58	44,883	1.29	19	44,986	0.42	315	14,071	22.39
Gender									
Female	163	317,201	0.51	53	317,480	0.17	----	----	----
Male	101	98,420	1.03	32	98,560	0.32	1,428	95,647	14.93
Alcohol Use / Abuse									
Yes	1	1,521	0.66	1	1,523	0.66	7	600	11.67
No	263	414,101	0.64	84	414,517	0.20	1,421	95,047	14.95
Smoking									
Yes	6	9,702	0.62	2	9,715	0.21	61	2,661	22.92
No	258	405,919	0.64	83	406,325	0.20	1,367	92,985	14.70
Overweight / Obesity									
Yes	4	16,298	0.25	1	16,305	0.06	51	3,029	16.84
No	260	399,324	0.65	84	399,735	0.21	1,377	92,618	14.87
Chronic Obstructive Pulmonary Disease									
Yes	9	9,558	0.94	1	9,559	0.10	61	3,071	19.86
No	255	406,064	0.63	84	406,481	0.21	1,367	92,576	14.77
Renal Impairment / Dialysis									
Yes	19	8,471	2.24	7	8,488	0.82	71	3,696	19.21
No	245	407,151	0.60	78	407,551	0.19	1,357	91,950	14.76

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Non-hodgkin's Lymphoma			Pancreas			Prostate (Men only)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Diabetes									
Yes	37	34,516	1.07	15	34,554	0.43	196	11,167	17.55
No	227	381,106	0.60	70	381,486	0.18	1,232	84,480	14.58
Endometrial Polyps (Women only)									
Yes	0	536	0.00	0	536	0.00	----	----	----
No	163	316,665	0.05	53	316,944	0.02	----	----	----
Irritable Bowel Syndrome									
Yes	5	7,914	0.63	0	7,929	0.00	16	909	17.59
No	259	407,708	0.64	85	408,111	0.21	1,412	94,737	14.90
Polycystic Ovary Syndrome (Women only)									
Yes	0	799	0.00	0	799	0.00	----	----	----
No	163	316,402	0.05	53	316,681	0.02	----	----	----
Any Cancer Drug									
Yes	15	17,171	0.87	7	17,198	0.41	88	1,641	53.64
No	249	398,450	0.62	78	398,842	0.20	1,340	94,006	14.25
Alkylating Agents									
Yes	0	141	0.00	1	141	7.10	1	54	18.55
No	264	415,481	0.64	84	415,899	0.20	1,427	95,593	14.93
Antimetabolites									
Yes	4	4,509	0.89	5	4,519	1.11	13	881	14.75
No	260	411,113	0.63	80	411,521	0.19	1,415	94,765	14.93

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Non-hodgkin's Lymphoma			Pancreas			Prostate (Men only)		
	Cases	Person-years[†]	IR[‡]	Cases	Person-years[†]	IR[‡]	Cases	Person-years[†]	IR[‡]
Antimicrotubule Agents									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	264	415,622	0.64	85	416,040	0.20	1,428	95,647	14.93
Topoisomerase-active Agents									
Yes	0	4	0.00	0	4	0.00	0	1	0.00
No	264	415,618	0.64	85	416,036	0.20	1,428	95,646	14.93
Antineoplastic Antibiotics									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	264	415,622	0.64	85	416,040	0.20	1,428	95,647	14.93
Endocrine Agents									
Yes	10	12,491	0.80	2	12,502	0.16	77	633	121.59
No	254	403,131	0.63	83	403,538	0.21	1,351	95,013	14.22
Biologically-directed Therapies									
Yes	0	133	0.00	0	133	0.00	0	56	0.00
No	264	415,489	0.64	85	415,907	0.20	1,428	95,591	14.94
Immune Therapies									
Yes	2	91	22.05	0	98	0.00	0	38	0.00
No	262	415,531	0.63	85	415,942	0.20	1,428	95,608	14.94
Miscellaneous Agents									
Yes	0	13	0.00	0	13	0.00	0	2	0.00
No	264	415,609	0.64	85	416,027	0.20	1,428	95,644	14.93

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

[†] Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

[‡] IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified Cancer First Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Uterus (Women only)			Any of Top 10 cancers		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	108	317,360	0.34	4,612	407,539	11.32
Age						
18-44	3	75,252	0.04	180	92,793	1.94
45-54	20	93,246	0.21	720	111,260	6.47
55-64	47	89,833	0.52	1,789	117,554	15.22
65-74	20	28,868	0.69	971	42,761	22.71
75+	18	30,162	0.60	952	43,171	22.05
Gender						
Female	108	317,360	0.34	2,204	313,479	7.03
Male	----	----	----	2,408	94,061	25.60
Alcohol Use / Abuse						
Yes	1	913	1.10	28	1,484	18.86
No	107	316,448	0.34	4,584	406,055	11.29
Smoking						
Yes	1	6,954	0.14	195	9,406	20.73
No	107	310,407	0.34	4,417	398,133	11.09
Overweight / Obesity						
Yes	9	13,165	0.68	166	16,022	10.36
No	99	304,195	0.33	4,446	391,518	11.36
Chronic Obstructive Pulmonary Disease						
Yes	1	6,383	0.16	229	9,226	24.82
No	107	310,977	0.34	4,383	398,313	11.00
Renal Impairment / Dialysis						
Yes	4	4,662	0.86	217	8,181	26.53
No	104	312,698	0.33	4,395	399,358	11.01

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified Cancer First Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Uterus (Women only)			Any of Top 10 cancers		
	Cases	Person-years[†]	IR[‡]	Cases	Person-years[†]	IR[‡]
Diabetes						
Yes	14	23,003	0.61	598	33,574	17.81
No	94	294,358	0.32	4,014	373,965	10.73
Endometrial Polyps (Women only)						
Yes	0	536	0.00	4	529	7.56
No	108	316,824	0.03	2,200	312,950	0.70
Irritable Bowel Syndrome						
Yes	1	6,977	0.14	53	7,829	6.77
No	107	310,383	0.34	4,559	399,710	11.41
Polycystic Ovary Syndrome (Women only)						
Yes	0	799	0.00	0	799	0.00
No	108	316,561	0.03	2,204	312,680	0.70
Any Cancer Drug						
Yes	14	15,338	0.91	377	16,488	22.87
No	94	302,023	0.31	4,235	391,051	10.83
Alkylating Agents						
Yes	0	85	0.00	6	138	43.54
No	108	317,275	0.34	4,606	407,401	11.31
Antimetabolites						
Yes	0	3,602	0.00	70	4,407	15.88
No	108	313,758	0.34	4,542	403,132	11.27

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

[†] Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

[‡] IR: Incidence Rate per 1,000 person-years

Table C2. Incidence of Claims-Identified Cancer First Outcomes by Select Baseline* Characteristics, Any Time after Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Uterus (Women only)			Any of Top 10 cancers		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Antimicrotubule Agents						
Yes	0	0	0.00	0	0	0.00
No	108	317,360	0.34	4,612	407,539	11.32
Topoisomerase-active Agents						
Yes	0	4	0.00	0	4	0.00
No	108	317,357	0.34	4,612	407,535	11.32
Antineoplastic Antibiotics						
Yes	0	0	0.00	0	0	0.00
No	108	317,360	0.34	4,612	407,539	11.32
Endocrine Agents						
Yes	14	11,681	1.20	303	11,911	25.44
No	94	305,680	0.31	4,309	395,628	10.89
Biologically-directed Therapies						
Yes	0	77	0.00	4	127	31.58
No	108	317,283	0.34	4,608	407,412	11.31
Immune Therapies						
Yes	0	59	0.00	5	85	59.12
No	108	317,301	0.34	4,607	407,454	11.31
Miscellaneous Agents						
Yes	0	10	0.00	0	13	0.00
No	108	317,350	0.34	4,612	407,526	11.32

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Bladder			Breast (Women only)			Colon/Rectum		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	296	89,050	3.32	334	58,401	5.72	143	89,350	1.60
Age									
65-74	137	44,304	3.09	166	28,554	5.81	57	44,488	1.28
75+	159	44,746	3.55	168	29,846	5.63	86	44,862	1.92
Gender									
Female	96	58,935	1.63	334	58,401	5.72	87	58,938	1.48
Male	200	30,115	6.64	----	----	----	56	30,412	1.84
Alcohol Use / Abuse									
Yes	1	307	3.25	1	168	5.97	0	308	0.00
No	295	88,743	3.32	333	58,233	5.72	143	89,042	1.61
Smoking									
Yes	14	1,140	12.28	2	656	3.05	0	1,159	0.00
No	282	87,910	3.21	332	57,745	5.75	143	88,192	1.62
Overweight / Obesity									
Yes	3	2,092	1.43	4	1,402	2.85	4	2,090	1.91
No	293	86,958	3.37	330	56,999	5.79	139	87,260	1.59
Chronic Obstructive Pulmonary Disease									
Yes	40	4,860	8.23	14	2,925	4.79	10	4,912	2.04
No	256	84,190	3.04	320	55,476	5.77	133	84,438	1.58
Renal Impairment / Dialysis									
Yes	21	4,140	5.07	8	2,249	3.56	11	4,161	2.64
No	275	84,910	3.24	326	56,152	5.81	132	85,189	1.55

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Bladder			Breast (Women only)			Colon/Rectum		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Diabetes									
Yes	46	12,375	3.72	49	7,134	6.87	30	12,408	2.42
No	250	76,676	3.26	285	51,266	5.56	113	76,943	1.47
Endometrial Polyps (Women only)									
Yes	0	44	0.00	2	41	48.44	0	44	0.00
No	96	58,891	0.16	332	58,360	0.57	87	58,894	0.15
Irritable Bowel Syndrome									
Yes	2	1,354	1.48	6	1,089	5.51	1	1,355	0.74
No	294	87,696	3.35	328	57,312	5.72	142	87,995	1.61
Polycystic Ovary Syndrome (Women only)									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	96	58,935	0.16	334	58,401	0.57	87	58,938	0.15
Any Cancer Drug									
Yes	15	5,872	2.55	83	4,722	17.58	9	5,891	1.53
No	281	83,178	3.38	251	53,679	4.68	134	83,459	1.61
Alkylating Agents									
Yes	0	65	0.00	0	40	0.00	1	65	15.45
No	296	88,985	3.33	334	58,361	5.72	142	89,286	1.59
Antimetabolites									
Yes	7	1,561	4.48	10	1,112	9.00	2	1,567	1.28
No	289	87,489	3.30	324	57,289	5.66	141	87,784	1.61

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Bladder			Breast (Women only)			Colon/Rectum		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Antimicrotubule Agents									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	296	89,050	3.32	334	58,401	5.72	143	89,350	1.60
Topoisomerase-active Agents									
Yes	0	2	0.00	0	2	0.00	0	2	0.00
No	296	89,049	3.32	334	58,399	5.72	143	89,349	1.60
Antineoplastic Antibiotics									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	296	89,050	3.32	334	58,401	5.72	143	89,350	1.60
Endocrine Agents									
Yes	6	4,229	1.42	76	3,573	21.27	6	4,239	1.42
No	290	84,822	3.42	258	54,828	4.71	137	85,111	1.61
Biologically-directed Therapies									
Yes	0	38	0.00	1	16	61.44	0	38	0.00
No	296	89,012	3.33	333	58,384	5.70	143	89,312	1.60
Immune Therapies									
Yes	2	45	44.11	0	25	0.00	0	49	0.00
No	294	89,005	3.30	334	58,375	5.72	143	89,302	1.60
Miscellaneous Agents									
Yes	0	4	0.00	0	4	0.00	0	4	0.00
No	296	89,046	3.32	334	58,396	5.72	143	89,346	1.60

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Kidney/Renal Pelvis			Lung/Bronchus			Melanoma		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	65	89,443	0.73	189	89,380	2.11	36	89,517	0.40
Age									
65-74	38	44,503	0.85	97	44,483	2.18	14	44,553	0.31
75+	27	44,940	0.60	92	44,896	2.05	22	44,965	0.49
Gender									
Female	31	59,027	0.53	102	58,975	1.73	16	59,056	0.27
Male	34	30,416	1.12	87	30,404	2.86	20	30,461	0.66
Alcohol Use / Abuse									
Yes	2	308	6.50	3	306	9.81	0	308	0.00
No	63	89,135	0.71	186	89,074	2.09	36	89,209	0.40
Smoking									
Yes	3	1,154	2.60	8	1,151	6.95	0	1,159	0.00
No	62	88,289	0.70	181	88,228	2.05	36	88,359	0.41
Overweight / Obesity									
Yes	1	2,092	0.48	7	2,083	3.36	1	2,095	0.48
No	64	87,351	0.73	182	87,296	2.08	35	87,423	0.40
Chronic Obstructive Pulmonary Disease									
Yes	4	4,915	0.81	36	4,891	7.36	2	4,923	0.41
No	61	84,528	0.72	153	84,488	1.81	34	84,594	0.40
Renal Impairment / Dialysis									
Yes	8	4,156	1.92	10	4,161	2.40	2	4,167	0.48
No	57	85,287	0.67	179	85,218	2.10	34	85,350	0.40

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Kidney/Renal Pelvis			Lung/Bronchus			Melanoma		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Diabetes									
Yes	15	12,420	1.21	28	12,420	2.25	4	12,440	0.32
No	50	77,023	0.65	161	76,959	2.09	32	77,077	0.42
Endometrial Polyps (Women only)									
Yes	0	44	0.00	0	44	0.00	0	44	0.00
No	31	58,983	0.05	102	58,931	0.17	16	59,012	0.03
Irritable Bowel Syndrome									
Yes	2	1,352	1.48	4	1,349	2.96	0	1,356	0.00
No	63	88,091	0.72	185	88,030	2.10	36	88,162	0.41
Polycystic Ovary Syndrome (Women only)									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	31	59,027	0.05	102	58,975	0.17	16	59,056	0.03
Any Cancer Drug									
Yes	6	5,888	1.02	19	5,887	3.23	2	5,901	0.34
No	59	83,555	0.71	170	83,492	2.04	34	83,616	0.41
Alkylating Agents									
Yes	0	65	0.00	1	65	15.36	1	65	15.43
No	65	89,378	0.73	188	89,314	2.10	35	89,453	0.39
Antimetabolites									
Yes	3	1,559	1.92	4	1,565	2.56	0	1,568	0.00
No	62	87,884	0.71	185	87,815	2.11	36	87,949	0.41

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Kidney/Renal Pelvis			Lung/Bronchus			Melanoma		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Antimicrotubule Agents									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	65	89,443	0.73	189	89,380	2.11	36	89,517	0.40
Topoisomerase-active Agents									
Yes	0	2	0.00	0	2	0.00	0	2	0.00
No	65	89,441	0.73	189	89,378	2.11	36	89,516	0.40
Antineoplastic Antibiotics									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	65	89,443	0.73	189	89,380	2.11	36	89,517	0.40
Endocrine Agents									
Yes	3	4,242	0.71	13	4,237	3.07	1	4,247	0.24
No	62	85,201	0.73	176	85,143	2.07	35	85,270	0.41
Biologically-directed Therapies									
Yes	0	38	0.00	1	38	26.43	0	38	0.00
No	65	89,405	0.73	188	89,342	2.10	36	89,479	0.40
Immune Therapies									
Yes	0	49	0.00	0	49	0.00	0	49	0.00
No	65	89,394	0.73	189	89,331	2.12	36	89,469	0.40
Miscellaneous Agents									
Yes	0	4	0.00	0	4	0.00	0	4	0.00
No	65	89,439	0.73	189	89,375	2.11	36	89,513	0.40

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Non-Hodgkin's Lymphoma			Pancreas			Prostate (Men only)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	111	89,345	1.24	42	89,530	0.47	683	28,987	23.56
Age									
65-74	53	44,462	1.19	23	44,544	0.52	368	14,916	24.67
75+	58	44,883	1.29	19	44,986	0.42	315	14,071	22.39
Gender									
Female	64	58,948	1.09	27	59,065	0.46	----	----	----
Male	47	30,397	1.55	15	30,464	0.49	683	28,987	23.56
Alcohol Use / Abuse									
Yes	0	308	0.00	0	308	0.00	2	139	14.36
No	111	89,037	1.25	42	89,221	0.47	681	28,848	23.61
Smoking									
Yes	0	1,159	0.00	0	1,159	0.00	14	471	29.73
No	111	88,186	1.26	42	88,371	0.48	669	28,516	23.46
Overweight / Obesity									
Yes	2	2,092	0.96	0	2,096	0.00	11	669	16.44
No	109	87,253	1.25	42	87,433	0.48	672	28,318	23.73
Chronic Obstructive Pulmonary Disease									
Yes	6	4,924	1.22	1	4,923	0.20	45	1,892	23.78
No	105	84,421	1.24	41	84,606	0.48	638	27,095	23.55
Renal Impairment / Dialysis									
Yes	9	4,153	2.17	6	4,160	1.44	53	1,812	29.25
No	102	85,192	1.20	36	85,370	0.42	630	27,175	23.18

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Non-Hodgkin's Lymphoma			Pancreas			Prostate (Men only)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Diabetes									
Yes	19	12,423	1.53	6	12,444	0.48	101	5,021	20.12
No	92	76,922	1.20	36	77,085	0.47	582	23,966	24.28
Endometrial Polyps (women only)									
Yes	0	44	0.00	0	44	0.00	----	----	----
No	64	58,904	0.11	27	59,021	0.05	----	----	----
Irritable Bowel Syndrome									
Yes	2	1,349	1.48	0	1,356	0.00	12	226	53.16
No	109	87,997	1.24	42	88,174	0.48	671	28,761	23.33
Polycystic Ovary Syndrome (women only)									
Yes	0	0	0.00	0	0	0.00	----	----	----
No	64	58,948	0.11	27	59,065	0.05	----	----	----
Any Cancer Drug									
Yes	9	5,882	1.53	4	5,897	0.68	59	864	68.29
No	102	83,463	1.22	38	83,633	0.45	624	28,123	22.19
Alkylating Agents									
Yes	0	65	0.00	0	65	0.00	1	24	42.12
No	111	89,280	1.24	42	89,464	0.47	682	28,963	23.55

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Non-Hodgkin's Lymphoma			Pancreas			Prostate (Men only)		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Antimetabolites									
Yes	2	1,567	1.28	2	1,568	1.28	8	421	19.00
No	109	87,778	1.24	40	87,962	0.45	675	28,566	23.63
Antimicrotubule Agents									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	111	89,345	1.24	42	89,530	0.47	683	28,987	23.56
Topoisomerase-active Agents									
Yes	0	2	0.00	0	2	0.00	0	0	0.00
No	111	89,343	1.24	42	89,528	0.47	683	28,987	23.56
Antineoplastic Antibiotics									
Yes	0	0	0.00	0	0	0.00	0	0	0.00
No	111	89,345	1.24	42	89,530	0.47	683	28,987	23.56
Endocrine Agents									
Yes	6	4,236	1.42	2	4,243	0.47	53	389	136.36
No	105	85,110	1.23	40	85,286	0.47	630	28,598	22.03
Biologically-directed Therapies									
Yes	0	38	0.00	0	38	0.00	0	17	0.00
No	111	89,307	1.24	42	89,491	0.47	683	28,969	23.58
Immune Therapies									
Yes	2	42	48.05	0	49	0.00	0	23	0.00
No	109	89,304	1.22	42	89,481	0.47	683	28,964	23.58
Miscellaneous Agents									
Yes	0	4	0.00	0	4	0.00	0	0	0.00
No	111	89,341	1.24	42	89,525	0.47	683	28,987	23.56

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Uterus (Women only)			Any of Top 10 cancers		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Overall	38	59,030	0.64	1,923	85,932	22.38
Age						
65-74	20	28,868	0.69	971	42,761	22.71
75+	18	30,162	0.60	952	43,171	22.05
Gender						
Female	38	59,030	0.64	790	57,663	13.70
Male	----	----	----	1,133	28,269	40.08
Alcohol Use / Abuse						
Yes	1	163	6.13	10	298	33.58
No	37	58,866	0.63	1,913	85,634	22.34
Smoking						
Yes	0	660	0.00	41	1,095	37.43
No	38	58,370	0.65	1,882	84,837	22.18
Overweight / Obesity						
Yes	2	1,405	1.42	34	2,035	16.71
No	36	57,624	0.62	1,889	83,897	22.52
Chronic Obstructive Pulmonary Disease						
Yes	1	2,954	0.34	157	4,686	33.51
No	37	56,075	0.66	1,766	81,247	21.74

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Uterus (Women only)			Any of Top 10 cancers		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Renal Impairment / Dialysis						
Yes	4	2,258	1.77	132	3,969	33.25
No	34	56,772	0.60	1,791	81,963	21.85
Diabetes						
Yes	3	7,216	0.42	301	11,944	25.20
No	35	51,813	0.68	1,622	73,988	21.92
Endometrial Polyps (women only)						
Yes	0	44	0.00	2	41	48.44
No	38	58,986	0.06	788	57,622	1.37
Irritable Bowel Syndrome						
Yes	1	1,092	0.92	30	1,292	23.22
No	37	57,938	0.64	1,893	84,640	22.37
Polycystic Ovary Syndrome (women only)						
Yes	0	0	0.00	0	0	0.00
No	38	59,030	0.06	790	57,663	1.37
Any Cancer Drug						
Yes	4	4,878	0.82	206	5,492	37.51
No	34	54,152	0.63	1,717	80,440	21.34
Alkylating Agents						
Yes	0	40	0.00	4	63	63.89
No	38	58,990	0.64	1,919	85,870	22.35

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C2.1. Incidence of Claims-Identified First Cancer Outcomes by Select Baseline* Characteristics, Any time after Index Date, Among Patients ≥ 65 Years at Index Date. Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Uterus (Women only)			Any of Top 10 cancers		
	Cases	Person-years†	IR‡	Cases	Person-years†	IR‡
Antimetabolites						
Yes	0	1,125	0.00	37	1,509	24.51
No	38	57,904	0.66	1,886	84,423	22.34
Antimicrotubule Agents						
Yes	0	0	0.00	0	0	0.00
No	38	59,030	0.64	1,923	85,932	22.38
Topoisomerase-active Agents						
Yes	0	2	0.00	0	2	0.00
No	38	59,028	0.64	1,923	85,930	22.38
Antineoplastic Antibiotics						
Yes	0	0	0.00	0	0	0.00
No	38	59,030	0.64	1,923	85,932	22.38
Endocrine Agents						
Yes	4	3,718	1.08	167	3,901	42.81
No	34	55,312	0.61	1,756	82,031	21.41
Biologically-directed Therapies						
Yes	0	21	0.00	2	33	59.78
No	38	59,009	0.64	1,921	85,899	22.36
Immune Therapies						
Yes	0	25	0.00	4	38	104.35
No	38	59,004	0.64	1,919	85,894	22.34
Miscellaneous Agents						
Yes	0	4	0.00	0	4	0.00
No	38	59,026	0.64	1,923	85,928	22.38

Abbreviations: IR, Incidence Rate

* Includes only patients who do not meet the definition for baseline cancer.

Baseline period began July 1, 2003.

† Follow-up time for each cancer outcome begins on the day after index dispensing the study drug and ends on the earliest of the following: first occurrence of any of the top 10 cancers, disenrollment from the health plan, death or end of study period.

‡ IR: Incidence Rate per 1,000 person-years

Table C3. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure", Optum Research Database: 01 January 2004 - 30 September 2012*

	Men						Women					
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Any of Top 10 Cancers														
Overall	2,408	94,061	25.60	----	---- - ----	----	---- - ----	2,204	313,479	7.03	----	---- - ----	----	---- - ----
Unexposed	1,794	70,433	25.47	Ref	---- - ----	----	---- - ----	1,576	222,388	7.09	Ref	---- - ----	----	---- - ----
All Drugs	614	23,628	25.99	1.02	0.93 - 1.12	0.84	0.76 - 0.92	628	91,091	6.89	0.97	0.89 - 1.07	0.81	0.74 - 0.89
Oxybutynin	156	6,683	23.34	0.92	0.78 - 1.08	0.80	0.68 - 0.94	153	23,513	6.51	0.92	0.78 - 1.08	0.77	0.65 - 0.91
Tolterodine	194	6,427	30.18	1.19	1.02 - 1.37	0.95	0.82 - 1.10	188	26,190	7.18	1.01	0.87 - 1.18	0.82	0.70 - 0.95
Solifenacin	147	5,927	24.80	0.97	0.82 - 1.15	0.80	0.67 - 0.94	158	24,812	6.37	0.90	0.76 - 1.06	0.77	0.65 - 0.90
Darifenacin	65	2,675	24.30	0.95	0.74 - 1.22	0.77	0.60 - 0.98	85	10,740	7.91	1.12	0.90 - 1.39	0.91	0.74 - 1.14
Fesoterodine	15	578	25.95	1.02	0.61 - 1.69	0.85	0.51 - 1.41	15	2,008	7.47	1.05	0.63 - 1.75	0.85	0.51 - 1.41
Trospium	37	1,338	27.64	1.09	0.78 - 1.50	0.86	0.62 - 1.19	29	3,828	7.58	1.07	0.74 - 1.54	0.87	0.60 - 1.26
Bladder														
Overall	498	97,696	5.10	----	---- - ----	----	---- - ----	200	317,176	0.63	----	---- - ----	----	---- - ----
Unexposed	395	73,427	5.38	Ref	---- - ----	----	---- - ----	160	225,230	0.71	Ref	---- - ----	----	---- - ----
All Drugs	103	24,269	4.24	0.79	0.64 - 0.98	0.68	0.55 - 0.85	40	91,946	0.44	0.61	0.43 - 0.87	0.49	0.34 - 0.69
Oxybutynin	43	6,826	6.30	1.17	0.85 - 1.60	1.06	0.78 - 1.46	11	23,736	0.46	0.65	0.35 - 1.20	0.53	0.29 - 0.97
Tolterodine	22	6,583	3.34	0.62	0.40 - 0.95	0.52	0.34 - 0.80	11	26,404	0.42	0.59	0.32 - 1.08	0.45	0.24 - 0.83
Solifenacin	25	6,111	4.09	0.76	0.51 - 1.14	0.65	0.43 - 0.97	7	25,049	0.28	0.39	0.18 - 0.84	0.33	0.15 - 0.69
Darifenacin	8	2,757	2.90	0.54	0.27 - 1.09	0.45	0.23 - 0.92	6	10,861	0.55	0.78	0.34 - 1.76	0.61	0.27 - 1.39
Fesoterodine	2	600	3.33	0.62	0.15 - 2.48	0.53	0.13 - 2.14	3	2,030	1.48	2.08	0.66 - 6.52	1.58	0.50 - 4.95
Trospium	3	1,393	2.15	0.40	0.13 - 1.25	0.33	0.11 - 1.02	2	3,865	0.52	0.73	0.18 - 2.94	0.56	0.14 - 2.28

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure", Optum Research Database: 01 January 2004 - 30 September 2012*

	Men						Women					
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Breast (Women only)														
Overall	----	----	----	----	---- - ----	----	---- - ----	1,144	315,222	3.63	----	---- - ----	----	---- - ----
Unexposed	----	----	----	----	---- - ----	----	---- - ----	792	223,787	3.54	Ref	---- - ----	----	---- - ----
All Drugs	----	----	----	----	---- - ----	----	---- - ----	352	91,435	3.85	1.09	0.96 - 1.23	0.94	0.82 - 1.06
Oxybutynin	----	----	----	----	---- - ----	----	---- - ----	82	23,623	3.47	0.98	0.78 - 1.23	0.85	0.68 - 1.07
Tolterodine	----	----	----	----	---- - ----	----	---- - ----	108	26,270	4.11	1.16	0.95 - 1.42	0.98	0.80 - 1.20
Solifenacin	----	----	----	----	---- - ----	----	---- - ----	89	24,893	3.58	1.01	0.81 - 1.26	0.88	0.71 - 1.10
Darifenacin	----	----	----	----	---- - ----	----	---- - ----	53	10,784	4.91	1.39	1.05 - 1.83	1.18	0.89 - 1.56
Fesoterodine	----	----	----	----	---- - ----	----	---- - ----	6	2,017	2.97	0.84	0.38 - 1.88	0.71	0.32 - 1.58
Trospium	----	----	----	----	---- - ----	----	---- - ----	14	3,847	3.64	1.03	0.61 - 1.74	0.88	0.52 - 1.49
Colon/Rectum														
Overall	111	98,449	1.13	----	---- - ----	----	---- - ----	181	317,198	0.57	----	---- - ----	----	---- - ----
Unexposed	84	74,148	1.13	Ref	---- - ----	----	---- - ----	131	225,288	0.58	Ref	---- - ----	----	---- - ----
All Drugs	27	24,301	1.11	0.98	0.64 - 1.51	0.82	0.53 - 1.28	50	91,910	0.54	0.94	0.68 - 1.30	0.75	0.54 - 1.04
Oxybutynin	3	6,839	0.44	0.39	0.12 - 1.22	0.34	0.11 - 1.08	11	23,730	0.46	0.80	0.43 - 1.47	0.66	0.35 - 1.21
Tolterodine	16	6,578	2.43	2.15	1.26 - 3.66	1.74	1.01 - 2.98	20	26,389	0.76	1.30	0.81 - 2.09	1.00	0.62 - 1.60
Solifenacin	4	6,123	0.65	0.58	0.21 - 1.57	0.49	0.18 - 1.35	5	25,047	0.20	0.34	0.14 - 0.84	0.29	0.12 - 0.72
Darifenacin	1	2,766	0.36	0.32	0.04 - 2.29	0.26	0.04 - 1.87	9	10,849	0.83	1.43	0.73 - 2.80	1.13	0.58 - 2.23
Fesoterodine	2	601	3.33	2.94	0.72 - 11.94	2.54	0.62 - 10.33	2	2,029	0.99	1.70	0.42 - 6.85	1.31	0.33 - 5.31
Trospium	1	1,394	0.72	0.63	0.09 - 4.55	0.49	0.07 - 3.51	3	3,866	0.78	1.33	0.42 - 4.19	1.04	0.33 - 3.25

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure", Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Kidney/Renal Pelvis														
Overall	86	98,444	0.87	----	---- - ----	----	---- - ----	84	317,368	0.26	----	---- - ----	----	---- - ----
Unexposed	63	74,135	0.85	Ref	---- - ----	----	---- - ----	64	225,420	0.28	Ref	---- - ----	----	---- - ----
All Drugs	23	24,309	0.95	1.11	0.69 - 1.79	0.98	0.61 - 1.59	20	91,948	0.22	0.77	0.46 - 1.27	0.63	0.38 - 1.04
Oxybutynin	5	6,836	0.73	0.86	0.35 - 2.14	0.80	0.32 - 1.99	4	23,738	0.17	0.59	0.22 - 1.63	0.50	0.18 - 1.36
Tolterodine	10	6,584	1.52	1.79	0.92 - 3.48	1.62	0.82 - 3.17	4	26,401	0.15	0.53	0.19 - 1.47	0.43	0.16 - 1.20
Solifenacin	4	6,129	0.65	0.77	0.28 - 2.11	0.67	0.24 - 1.85	7	25,052	0.28	0.98	0.45 - 2.15	0.83	0.38 - 1.81
Darifenacin	1	2,765	0.36	0.43	0.06 - 3.07	0.38	0.05 - 2.72	3	10,858	0.28	0.97	0.31 - 3.10	0.80	0.25 - 2.55
Fesoterodine	2	601	3.33	3.92	0.96 - 16.02	3.52	0.86 - 14.42	1	2,032	0.49	1.73	0.24 - 12.49	1.39	0.19 - 10.01
Trospium	1	1,393	0.72	0.84	0.12 - 6.09	0.74	0.10 - 5.35	1	3,867	0.26	0.91	0.13 - 6.57	0.75	0.10 - 5.38
Lung/Bronchus														
Overall	128	98,481	1.30	----	---- - ----	----	---- - ----	223	317,267	0.70	----	---- - ----	----	---- - ----
Unexposed	93	74,183	1.25	Ref	---- - ----	----	---- - ----	164	225,357	0.73	Ref	---- - ----	----	---- - ----
All Drugs	35	24,298	1.44	1.15	0.78 - 1.69	0.87	0.59 - 1.29	59	91,910	0.64	0.88	0.66 - 1.19	0.70	0.52 - 0.94
Oxybutynin	4	6,842	0.58	0.47	0.17 - 1.27	0.38	0.14 - 1.05	16	23,725	0.67	0.93	0.55 - 1.55	0.73	0.44 - 1.23
Tolterodine	15	6,577	2.28	1.82	1.05 - 3.14	1.35	0.78 - 2.34	20	26,388	0.76	1.04	0.65 - 1.66	0.79	0.49 - 1.25
Solifenacin	12	6,118	1.96	1.56	0.86 - 2.85	1.19	0.65 - 2.17	16	25,038	0.64	0.88	0.53 - 1.47	0.72	0.43 - 1.21
Darifenacin	3	2,764	1.09	0.87	0.27 - 2.73	0.63	0.20 - 2.01	5	10,861	0.46	0.63	0.26 - 1.54	0.49	0.20 - 1.19
Fesoterodine	0	603	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0	2,033	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	1	1,394	0.72	0.57	0.08 - 4.11	0.43	0.06 - 3.07	2	3,866	0.52	0.71	0.18 - 2.87	0.54	0.13 - 2.17

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure", Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [,¶]	95% CI
Melanoma														
Overall	38	98,548	0.39	----	---- - ----	----	---- - ----	59	317,383	0.19	----	---- - ----	----	---- - ----
Unexposed	26	74,227	0.35	Ref	---- - ----	----	---- - ----	42	225,447	0.19	Ref	---- - ----	----	---- - ----
All Drugs	12	24,321	0.49	1.41	0.71 - 2.79	1.17	0.59 - 2.34	17	91,936	0.18	0.99	0.57 - 1.74	0.89	0.50 - 1.57
Oxybutynin	3	6,842	0.44	1.25	0.38 - 4.14	1.12	0.34 - 3.71	6	23,724	0.25	1.36	0.58 - 3.19	1.23	0.52 - 2.89
Tolterodine	4	6,590	0.61	1.73	0.60 - 4.97	1.42	0.49 - 4.12	2	26,400	0.08	0.41	0.10 - 1.68	0.37	0.09 - 1.53
Solifenacin	3	6,126	0.49	1.40	0.42 - 4.62	1.23	0.37 - 4.08	6	25,050	0.24	1.29	0.55 - 3.02	1.18	0.50 - 2.79
Darifenacin	1	2,765	0.36	1.03	0.14 - 7.61	0.89	0.12 - 6.62	1	10,863	0.09	0.49	0.07 - 3.59	0.44	0.06 - 3.17
Fesoterodine	1	603	1.66	4.73	0.64 - 34.86	4.22	0.57 - 31.19	0	2,033	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	0	1,395	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	3,865	0.52	2.78	0.67 - 11.48	2.43	0.59 - 10.08
Non-hodgkin's Lymphoma														
Overall	101	98,420	1.03	----	---- - ----	----	---- - ----	163	317,201	0.51	----	---- - ----	----	---- - ----
Unexposed	75	74,117	1.01	Ref	---- - ----	----	---- - ----	111	225,305	0.49	Ref	---- - ----	----	---- - ----
All Drugs	26	24,303	1.07	1.06	0.68 - 1.65	0.91	0.58 - 1.43	52	91,896	0.57	1.15	0.83 - 1.60	0.94	0.67 - 1.30
Oxybutynin	7	6,838	1.02	1.01	0.47 - 2.19	0.91	0.42 - 1.98	17	23,715	0.72	1.46	0.87 - 2.42	1.19	0.71 - 1.98
Tolterodine	6	6,587	0.91	0.90	0.39 - 2.07	0.75	0.32 - 1.73	12	26,390	0.45	0.92	0.51 - 1.67	0.73	0.40 - 1.33
Solifenacin	9	6,120	1.47	1.45	0.73 - 2.90	1.24	0.62 - 2.48	14	25,034	0.56	1.14	0.65 - 1.98	0.94	0.54 - 1.65
Darifenacin	3	2,760	1.09	1.07	0.34 - 3.41	0.90	0.28 - 2.87	2	10,861	0.18	0.37	0.09 - 1.51	0.30	0.07 - 1.21
Fesoterodine	1	603	1.66	1.64	0.23 - 11.79	1.43	0.20 - 10.26	3	2,032	1.48	3.00	0.95 - 9.43	2.32	0.74 - 7.32
Trospium	0	1,395	0.00	0.00	0.00 - ----	0.00	0.00 - ----	4	3,863	1.04	2.10	0.78 - 5.70	1.66	0.61 - 4.51

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure", Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Pancreas														
Overall	32	98,560	0.32	----	---- - ----	----	---- - ----	53	317,480	0.17	----	---- - ----	----	---- - ----
Unexposed	23	74,235	0.31	Ref	---- - ----	----	---- - ----	41	225,514	0.18	Ref	---- - ----	----	---- - ----
All Drugs	9	24,325	0.37	1.19	0.55 - 2.58	1.02	0.47 2.21	12	91,966	0.13	0.72	0.38 - 1.37	0.56	0.29 - 1.07
Oxybutynin	2	6,843	0.29	0.94	0.22 - 4.00	0.84	0.20 3.56	0	23,742	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Tolterodine	3	6,587	0.46	1.47	0.44 - 4.90	1.24	0.37 4.17	1	26,408	0.04	0.21	0.03 - 1.51	0.16	0.02 - 1.15
Solifenacin	2	6,131	0.33	1.05	0.25 - 4.47	0.90	0.21 3.81	7	25,052	0.28	1.54	0.69 - 3.43	1.25	0.56 - 2.80
Darifenacin	2	2,765	0.72	2.33	0.55 - 9.90	2.01	0.47 8.56	3	10,864	0.28	1.52	0.47 - 4.90	1.18	0.36 - 3.81
Fesoterodine	0	604	0.00	0.00	0.00 - ----	0.00	0.00 ----	1	2,033	0.49	2.70	0.37 - 19.66	2.02	0.28 - 14.70
Trospium	0	1,395	0.00	0.00	0.00 - ----	0.00	0.00 ----	0	3,868	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Prostate (Men only)														
Overall	1,428	95,647	14.93	----	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Unexposed	1,046	71,806	14.57	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
All Drugs	382	23,841	16.02	1.10	0.98 - 1.24	0.90	0.80 1.01	----	----	----	----	---- - ----	----	---- - ----
Oxybutynin	91	6,733	13.52	0.93	0.75 - 1.15	0.81	0.65 1.00	----	----	----	----	---- - ----	----	---- - ----
Tolterodine	119	6,485	18.35	1.26	1.04 - 1.52	1.00	0.83 1.21	----	----	----	----	---- - ----	----	---- - ----
Solifenacin	88	5,997	14.67	1.01	0.81 - 1.25	0.82	0.66 1.02	----	----	----	----	---- - ----	----	---- - ----
Darifenacin	46	2,695	17.07	1.17	0.87 - 1.57	0.94	0.70 1.26	----	----	----	----	---- - ----	----	---- - ----
Fesoterodine	7	587	11.91	0.82	0.39 - 1.72	0.68	0.32 1.42	----	----	----	----	---- - ----	----	---- - ----
Trospium	31	1,344	23.07	1.58	1.11 - 2.26	1.26	0.88 1.80	----	----	----	----	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure", Optum Research Database: 01 January 2004 - 30 September 2012*

	Men						Women					
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Uterus (Women only)														
Overall	----	----	----	----	---- - ----	----	---- - ----	108	317,360	0.34	----	---- - ----	----	---- - ----
Unexposed	----	----	----	----	---- - ----	----	---- - ----	79	225,417	0.35	Ref	---- - ----	----	---- - ----
All Drugs	----	----	----	----	---- - ----	----	---- - ----	29	91,944	0.32	0.90	0.59 - 1.38	0.73	0.48 - 1.12
Oxybutynin	----	----	----	----	---- - ----	----	---- - ----	6	23,740	0.25	0.72	0.31 - 1.65	0.59	0.26 - 1.35
Tolterodine	----	----	----	----	---- - ----	----	---- - ----	11	26,398	0.42	1.19	0.63 - 2.23	0.97	0.51 - 1.82
Solifenacin	----	----	----	----	---- - ----	----	---- - ----	8	25,047	0.32	0.91	0.44 - 1.89	0.76	0.37 - 1.57
Darifenacin	----	----	----	----	---- - ----	----	---- - ----	3	10,862	0.28	0.79	0.25 - 2.50	0.63	0.20 - 1.99
Fesoterodine	----	----	----	----	---- - ----	----	---- - ----	0	2,033	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	----	----	----	----	---- - ----	----	---- - ----	1	3,863	0.26	0.74	0.10 - 5.31	0.60	0.08 - 4.30

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3.1. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure" Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Any of Top 10 Cancers														
Overall	1,133	28,269	40.08	----	---- - ----	----	---- - ----	790	57,663	13.70	----	---- - ----	----	---- - ----
Unexposed	776	18,566	41.80	Ref	---- - ----	----	---- - ----	532	36,100	14.74	Ref	---- - ----	----	---- - ----
All Drugs	357	9,703	36.79	0.88	0.78 - 1.00	0.88	0.78 - 1.00	258	21,564	11.96	0.81	0.70 - 0.94	0.81	0.70 - 0.94
Oxybutynin	84	2,470	34.01	0.81	0.65 - 1.02	0.81	0.65 - 1.02	64	5,330	12.01	0.81	0.63 - 1.06	0.81	0.63 - 1.06
Tolterodine	116	2,908	39.89	0.95	0.79 - 1.16	0.96	0.79 - 1.17	80	7,099	11.27	0.76	0.60 - 0.97	0.77	0.60 - 0.97
Solifenacin	84	2,315	36.28	0.87	0.69 - 1.09	0.87	0.69 - 1.09	57	5,134	11.10	0.75	0.57 - 0.99	0.75	0.57 - 0.99
Darifenacin	41	1,178	34.81	0.83	0.61 - 1.14	0.84	0.61 - 1.14	37	2,493	14.84	1.01	0.72 - 1.41	1.01	0.72 - 1.41
Fesoterodine	7	217	32.30	0.77	0.37 - 1.63	0.77	0.37 - 1.63	7	525	13.34	0.91	0.43 - 1.91	0.90	0.43 - 1.90
Trospium	25	615	40.64	0.97	0.65 - 1.45	0.98	0.66 - 1.47	13	984	13.22	0.90	0.52 - 1.55	0.90	0.52 - 1.56
Bladder														
Overall	200	30,115	6.64	----	---- - ----	----	---- - ----	96	58,935	1.63	----	---- - ----	----	---- - ----
Unexposed	151	20,004	7.55	Ref	---- - ----	----	---- - ----	71	37,006	1.92	Ref	---- - ----	----	---- - ----
All Drugs	49	10,111	4.85	0.64	0.47 - 0.89	0.63	0.46 - 0.87	25	21,929	1.14	0.59	0.38 - 0.94	0.59	0.38 - 0.94
Oxybutynin	15	2,564	5.85	0.78	0.46 - 1.32	0.77	0.45 - 1.31	6	5,415	1.11	0.58	0.25 - 1.33	0.58	0.25 - 1.33
Tolterodine	12	3,006	3.99	0.53	0.29 - 0.95	0.52	0.29 - 0.93	6	7,201	0.83	0.43	0.19 - 1.00	0.44	0.19 - 1.00
Solifenacin	13	2,429	5.35	0.71	0.40 - 1.25	0.71	0.40 - 1.25	6	5,224	1.15	0.60	0.26 - 1.38	0.59	0.26 - 1.35
Darifenacin	4	1,234	3.24	0.43	0.16 - 1.16	0.43	0.16 - 1.15	3	2,551	1.18	0.61	0.19 - 1.95	0.61	0.19 - 1.95
Fesoterodine	2	232	8.63	1.14	0.28 - 4.62	1.14	0.28 - 4.61	2	537	3.73	1.94	0.48 - 7.92	1.93	0.47 - 7.88
Trospium	3	647	4.64	0.61	0.20 - 1.93	0.60	0.19 - 1.88	2	1,001	2.00	1.04	0.26 - 4.24	1.05	0.26 - 4.27

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline

Table C3.1. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure" Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Breast (Women only)														
Overall	----	----	----	----	---- - ----	----	---- - ----	334	58,401	5.72	----	---- - ----	----	---- - ----
Unexposed	----	----	----	----	---- - ----	----	---- - ----	213	36,662	5.81	Ref	---- - ----	----	---- - ----
All Drugs	----	----	----	----	---- - ----	----	---- - ----	121	21,738	5.57	0.96	0.77 - 1.20	0.96	0.77 - 1.20
Oxybutynin	----	----	----	----	---- - ----	----	---- - ----	27	5,379	5.02	0.86	0.58 - 1.29	0.86	0.58 - 1.29
Tolterodine	----	----	----	----	---- - ----	----	---- - ----	47	7,141	6.58	1.13	0.83 - 1.55	1.13	0.83 - 1.56
Solifenacin	----	----	----	----	---- - ----	----	---- - ----	25	5,172	4.83	0.83	0.55 - 1.26	0.82	0.54 - 1.25
Darifenacin	----	----	----	----	---- - ----	----	---- - ----	18	2,520	7.14	1.23	0.76 - 1.99	1.23	0.76 - 1.99
Fesoterodine	----	----	----	----	---- - ----	----	---- - ----	2	529	3.78	0.65	0.16 - 2.62	0.65	0.16 - 2.61
Trospium	----	----	----	----	---- - ----	----	---- - ----	2	997	2.01	0.35	0.09 - 1.39	0.35	0.09 - 1.40
Colon/Rectum														
Overall	56	30,412	1.84	----	---- - ----	----	---- - ----	87	58,938	1.48	----	---- - ----	----	---- - ----
Unexposed	40	20,288	1.97	Ref	---- - ----	----	---- - ----	59	37,025	1.59	Ref	---- - ----	----	---- - ----
All Drugs	16	10,124	1.58	0.80	0.45 - 1.43	0.79	0.44 - 1.41	28	21,913	1.28	0.80	0.51 - 1.26	0.81	0.51 - 1.26
Oxybutynin	2	2,569	0.78	0.39	0.10 - 1.63	0.39	0.09 - 1.61	5	5,414	0.92	0.58	0.23 - 1.44	0.58	0.23 - 1.45
Tolterodine	9	3,001	3.00	1.52	0.74 - 3.13	1.46	0.71 - 3.02	11	7,196	1.53	0.96	0.50 - 1.83	0.95	0.50 - 1.81
Solifenacin	3	2,433	1.23	0.63	0.19 - 2.02	0.63	0.19 - 2.03	3	5,227	0.57	0.36	0.11 - 1.15	0.37	0.12 - 1.19
Darifenacin	0	1,241	0.00	0.00	0.00 - ----	0.00	0.00 - ----	5	2,541	1.97	1.23	0.50 - 3.08	1.23	0.49 - 3.07
Fesoterodine	2	232	8.61	4.37	1.06 - 18.06	4.32	1.04 - 17.89	2	533	3.76	2.36	0.58 - 9.65	2.39	0.58 - 9.76
Trospium	0	647	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	1,003	1.99	1.25	0.31 - 5.12	1.24	0.30 - 5.06

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3.1. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure" Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Kidney/Renal Pelvis														
Overall	34	30,416	1.12	----	---- - ----	----	---- - ----	31	59,027	0.53	----	---- - ----	----	---- - ----
Unexposed	21	20,282	1.04	Ref	---- - ----	----	---- - ----	23	37,089	0.62	Ref	---- - ----	----	---- - ----
All Drugs	13	10,134	1.28	1.24	0.62 - 2.47	1.24	0.62 - 2.47	8	21,938	0.36	0.59	0.26 - 1.31	0.58	0.26 - 1.30
Oxybutynin	3	2,566	1.17	1.13	0.34 - 3.79	1.13	0.34 - 3.79	0	5,421	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Tolterodine	3	3,012	1.00	0.96	0.29 - 3.23	0.97	0.29 - 3.25	1	7,199	0.14	0.22	0.03 - 1.66	0.23	0.03 - 1.68
Solifenacin	4	2,437	1.64	1.59	0.54 - 4.62	1.58	0.54 - 4.62	4	5,227	0.77	1.23	0.43 - 3.57	1.18	0.41 - 3.42
Darifenacin	1	1,241	0.81	0.78	0.10 - 5.79	0.78	0.10 - 5.81	2	2,551	0.78	1.26	0.30 - 5.36	1.27	0.30 - 5.37
Fesoterodine	1	232	4.31	4.16	0.56 - 30.94	4.18	0.56 - 31.08	0	536	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	1	646	1.55	1.50	0.20 - 11.12	1.51	0.20 - 11.27	1	1,004	1.00	1.61	0.22 - 11.90	1.64	0.22 - 12.12
Lung/Bronchus														
Overall	87	30,404	2.86	----	---- - ----	----	---- - ----	102	58,975	1.73	----	---- - ----	----	---- - ----
Unexposed	59	20,280	2.91	Ref	---- - ----	----	---- - ----	74	37,057	2.00	Ref	---- - ----	----	---- - ----
All Drugs	28	10,125	2.77	0.95	0.61 - 1.49	0.97	0.62 - 1.52	28	21,918	1.28	0.64	0.41 - 0.99	0.64	0.42 - 0.99
Oxybutynin	3	2,573	1.17	0.40	0.13 - 1.28	0.41	0.13 - 1.30	10	5,415	1.85	0.92	0.48 - 1.79	0.93	0.48 - 1.80
Tolterodine	10	3,001	3.33	1.15	0.59 - 2.24	1.20	0.62 - 2.36	8	7,191	1.11	0.56	0.27 - 1.16	0.55	0.27 - 1.15
Solifenacin	11	2,430	4.53	1.56	0.82 - 2.96	1.55	0.82 - 2.96	7	5,218	1.34	0.67	0.31 - 1.46	0.68	0.31 - 1.48
Darifenacin	3	1,240	2.42	0.83	0.26 - 2.65	0.85	0.27 - 2.72	2	2,553	0.78	0.39	0.10 - 1.60	0.39	0.10 - 1.60
Fesoterodine	0	235	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0	537	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	1	646	1.55	0.53	0.07 - 3.84	0.58	0.08 - 4.16	1	1,004	1.00	0.50	0.07 - 3.59	0.50	0.07 - 3.56

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3.1. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure" Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Melanoma														
Overall	20	30,461	0.66	----	---- - ----	----	---- - ----	16	59,056	0.27	----	---- - ----	----	---- - ----
Unexposed	10	20,322	0.49	Ref	---- - ----	----	---- - ----	9	37,126	0.24	Ref	---- - ----	----	---- - ----
All Drugs	10	10,140	0.99	2.00	0.83 - 4.81	1.99	0.83 - 4.77	7	21,930	0.32	1.32	0.49 - 3.54	1.33	0.49 - 3.57
Oxybutynin	3	2,573	1.17	2.37	0.65 - 8.61	2.34	0.64 - 8.49	1	5,414	0.18	0.76	0.10 - 6.01	0.77	0.10 - 6.09
Tolterodine	4	3,011	1.33	2.70	0.85 - 8.61	2.64	0.83 - 8.43	0	7,198	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Solifenacin	2	2,435	0.82	1.67	0.37 - 7.62	1.67	0.37 - 7.62	3	5,228	0.57	2.37	0.64 - 8.74	2.53	0.68 - 9.36
Darifenacin	1	1,240	0.81	1.64	0.21 - 12.80	1.64	0.21 - 12.85	1	2,552	0.39	1.62	0.20 - 12.76	1.61	0.20 - 12.72
Fesoterodine	0	235	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0	537	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	0	647	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	1,001	2.00	8.24	1.78 - 38.15	8.07	1.74 - 37.35
Non-hodgkin's Lymphoma														
Overall	47	30,397	1.55	----	---- - ----	----	---- - ----	64	58,948	1.09	----	---- - ----	----	---- - ----
Unexposed	34	20,262	1.68	Ref	---- - ----	----	---- - ----	43	37,046	1.16	Ref	---- - ----	----	---- - ----
All Drugs	13	10,135	1.28	0.76	0.40 - 1.45	0.76	0.40 - 1.43	21	21,902	0.96	0.83	0.49 - 1.39	0.83	0.49 - 1.39
Oxybutynin	4	2,572	1.56	0.93	0.33 - 2.61	0.92	0.33 - 2.61	10	5,401	1.85	1.60	0.80 - 3.17	1.59	0.80 - 3.17
Tolterodine	3	3,011	1.00	0.59	0.18 - 1.93	0.59	0.18 - 1.93	5	7,191	0.70	0.60	0.24 - 1.51	0.60	0.24 - 1.52
Solifenacin	5	2,435	2.05	1.22	0.48 - 3.13	1.22	0.48 - 3.13	2	5,221	0.38	0.33	0.08 - 1.36	0.33	0.08 - 1.35
Darifenacin	0	1,237	0.00	0.00	0.00 - ----	0.00	0.00 - ----	1	2,552	0.39	0.34	0.05 - 2.45	0.34	0.05 - 2.45
Fesoterodine	1	234	4.27	2.55	0.35 - 18.59	2.54	0.35 - 18.58	1	536	1.86	1.61	0.22 - 11.66	1.60	0.22 - 11.65
Trospium	0	647	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	1,002	2.00	1.72	0.42 - 7.10	1.72	0.42 - 7.11

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3.1. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure" Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Pancreas														
Overall	15	30,464	0.49	----	---- - ----	----	---- - ----	27	59,065	0.46	----	---- - ----	----	---- - ----
Unexposed	10	20,320	0.49	Ref	---- - ----	----	---- - ----	19	37,122	0.51	Ref	---- - ----	----	---- - ----
All Drugs	5	10,145	0.49	1.00	0.34 - 2.93	1.02	0.35 - 2.97	8	21,944	0.36	0.71	0.31 - 1.63	0.71	0.31 - 1.62
Oxybutynin	2	2,573	0.78	1.58	0.35 - 7.21	1.59	0.35 - 7.26	0	5,420	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Tolterodine	2	3,008	0.66	1.35	0.30 - 6.17	1.42	0.31 - 6.47	0	7,203	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Solifenacin	1	2,440	0.41	0.83	0.11 - 6.50	0.83	0.11 - 6.50	5	5,227	0.96	1.87	0.70 - 5.01	1.83	0.68 - 4.90
Darifenacin	0	1,241	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	2,553	0.78	1.53	0.36 - 6.57	1.53	0.36 - 6.57
Fesoterodine	0	235	0.00	0.00	0.00 - ----	0.00	0.00 - ----	1	537	1.86	3.64	0.49 - 27.17	3.62	0.48 - 27.05
Trospium	0	647	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0	1,004	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Prostate (Men only)														
Overall	683	28,987	23.56	----	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Unexposed	457	19,139	23.88	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
All Drugs	226	9,848	22.95	0.96	0.82 - 1.13	0.96	0.82 - 1.13	----	----	----	----	---- - ----	----	---- - ----
Oxybutynin	54	2,502	21.58	0.90	0.68 - 1.20	0.91	0.68 - 1.20	----	----	----	----	---- - ----	----	---- - ----
Tolterodine	74	2,946	25.12	1.05	0.82 - 1.34	1.07	0.83 - 1.37	----	----	----	----	---- - ----	----	---- - ----
Solifenacin	45	2,363	19.05	0.80	0.59 - 1.08	0.80	0.59 - 1.08	----	----	----	----	---- - ----	----	---- - ----
Darifenacin	32	1,193	26.82	1.12	0.78 - 1.61	1.13	0.79 - 1.62	----	----	----	----	---- - ----	----	---- - ----
Fesoterodine	1	225	4.44	0.19	0.03 - 1.32	0.19	0.03 - 1.33	----	----	----	----	---- - ----	----	---- - ----
Trospium	20	618	32.34	1.35	0.87 - 2.12	1.39	0.89 - 2.17	----	----	----	----	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C3.1. Crude and Adjusted Association between Antimuscarinic Drugs and Claims-Identified First Cancer Outcomes after Cohort Entry (Index drug use), Based on "Current Exposure" Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Uterus (Women only)														
Overall	----	----	----	----	---- - ----	----	---- - ----	38	59,030	0.64	----	---- - ----	----	---- - ----
Unexposed	----	----	----	----	---- - ----	----	---- - ----	23	37,098	0.62	Ref	---- - ----	----	---- - ----
All Drugs	----	----	----	----	---- - ----	----	---- - ----	15	21,932	0.68	1.10	0.58 - 2.11	1.10	0.57 - 2.11
Oxybutynin	----	----	----	----	---- - ----	----	---- - ----	5	5,417	0.92	1.49	0.57 - 3.92	1.48	0.56 - 3.90
Tolterodine	----	----	----	----	---- - ----	----	---- - ----	3	7,201	0.42	0.67	0.20 - 2.24	0.68	0.20 - 2.26
Solifenacin	----	----	----	----	---- - ----	----	---- - ----	3	5,227	0.57	0.93	0.28 - 3.08	0.91	0.27 - 3.02
Darifenacin	----	----	----	----	---- - ----	----	---- - ----	3	2,551	1.18	1.90	0.57 - 6.32	1.90	0.57 - 6.32
Fesoterodine	----	----	----	----	---- - ----	----	---- - ----	0	537	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Trospium	----	----	----	----	---- - ----	----	---- - ----	1	1,000	1.00	1.61	0.22 - 11.95	1.63	0.22 - 12.07

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: end of patient use (defined by dispensing amount + 7 day grace period), disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Any of Top 10 Cancers														
All Drugs	2,408	94,061	25.60	----	---- - ----	----	---- - ----	2,204	313,479	7.03	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	990	35,398	27.97	1.16	1.07 - 1.25	1.27	1.17 - 1.38	673	90,741	7.42	1.08	0.99 - 1.18	1.11	1.01 - 1.21
Never exposed	1,418	58,663	24.17	Ref	---- - ----	----	---- - ----	1,531	222,738	6.87	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	808	34,173	23.64	0.89	0.81 - 0.96	0.84	0.77 - 0.92	881	129,015	6.83	0.95	0.87 - 1.04	0.95	0.87 - 1.03
Never exposed	1,600	59,888	26.72	Ref	---- - ----	----	---- - ----	1,323	184,463	7.17	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	446	19,193	23.24	0.89	0.80 - 0.98	0.84	0.76 - 0.93	474	72,189	6.57	0.92	0.83 - 1.01	0.91	0.82 - 1.00
Never exposed	1,962	74,867	26.21	Ref	---- - ----	----	---- - ----	1,730	241,290	7.17	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	218	10,009	21.78	0.84	0.73 - 0.96	0.76	0.66 - 0.88	270	35,745	7.55	1.08	0.96 - 1.23	1.02	0.90 - 1.16
Never exposed	2,190	84,052	26.06	Ref	---- - ----	----	---- - ----	1,934	277,733	6.96	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	48	1,617	29.68	1.16	0.87 - 1.55	1.09	0.82 - 1.45	41	5,380	7.62	1.09	0.80 - 1.48	1.01	0.74 - 1.38
Never exposed	2,360	92,443	25.53	Ref	---- - ----	----	---- - ----	2,163	308,099	7.02	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	106	5,053	20.98	0.81	0.67 - 0.99	0.72	0.59 - 0.88	100	13,967	7.16	1.02	0.83 - 1.25	0.95	0.78 - 1.17
Never exposed	2,302	89,008	25.86	Ref	---- - ----	----	---- - ----	2,104	299,512	7.02	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Bladder														
All Drugs	498	97,696	5.10	----	---- - ----	----	---- - ----	200	317,176	0.63	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	290	36,839	7.87	2.30	1.93 - 2.75	2.49	2.08 - 2.98	96	91,870	1.04	2.26	1.72 - 2.99	2.35	1.78 - 3.10
Never exposed	208	60,857	3.42	Ref	---- - ----	----	---- - ----	104	225,306	0.46	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	133	35,658	3.73	0.63	0.52 - 0.77	0.61	0.50 - 0.74	60	130,731	0.46	0.61	0.45 - 0.83	0.60	0.44 - 0.81
Never exposed	365	62,038	5.88	Ref	---- - ----	----	---- - ----	140	186,445	0.75	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	73	19,973	3.65	0.67	0.52 - 0.86	0.64	0.50 - 0.82	33	73,032	0.45	0.66	0.45 - 0.96	0.66	0.45 - 0.96
Never exposed	425	77,723	5.47	Ref	---- - ----	----	---- - ----	167	244,144	0.68	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	28	10,444	2.68	0.50	0.34 - 0.73	0.46	0.32 - 0.68	17	36,291	0.47	0.72	0.44 - 1.18	0.67	0.41 - 1.10
Never exposed	470	87,252	5.39	Ref	---- - ----	----	---- - ----	183	280,885	0.65	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	8	1,696	4.72	0.92	0.46 - 1.86	0.88	0.44 - 1.77	5	5,436	0.92	1.47	0.61 - 3.57	1.35	0.55 - 3.27
Never exposed	490	96,000	5.10	Ref	---- - ----	----	---- - ----	195	311,740	0.63	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	10	5,306	1.88	0.36	0.19 - 0.67	0.32	0.17 - 0.60	6	14,174	0.42	0.66	0.29 - 1.49	0.60	0.27 - 1.36
Never exposed	488	92,391	5.28	Ref	---- - ----	----	---- - ----	194	303,002	0.64	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men						Women					
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Breast (Women only)														
All Drugs	----	----	----	----	---- - ----	----	---- - ----	1,144	315,221	3.63	----	---- - ----	----	---- - ----
Oxybutynin	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	308	91,395	3.37	0.90	0.79 - 1.03	0.92	0.81 - 1.05
Never exposed	----	----	----	----	---- - ----	----	---- - ----	836	223,826	3.74	Ref	---- - ----	----	---- - ----
Tolterodine	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	459	129,779	3.54	0.96	0.85 - 1.08	0.96	0.85 - 1.08
Never exposed	----	----	----	----	---- - ----	----	---- - ----	685	185,443	3.69	Ref	---- - ----	----	---- - ----
Solifenacin	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	266	72,516	3.67	1.01	0.88 - 1.16	1.00	0.87 - 1.15
Never exposed	----	----	----	----	---- - ----	----	---- - ----	878	242,706	3.62	Ref	---- - ----	----	---- - ----
Darifenacin	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	147	36,008	4.08	1.14	0.96 - 1.36	1.09	0.91 - 1.29
Never exposed	----	----	----	----	---- - ----	----	---- - ----	997	279,213	3.57	Ref	---- - ----	----	---- - ----
Fesoterodine	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	19	5,409	3.51	0.97	0.61 - 1.52	0.91	0.58 - 1.44
Never exposed	----	----	----	----	---- - ----	----	---- - ----	1,125	309,813	3.63	Ref	---- - ----	----	---- - ----
Trospium	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	55	14,057	3.91	1.08	0.83 - 1.42	1.03	0.79 - 1.36
Never exposed	----	----	----	----	---- - ----	----	---- - ----	1,089	301,165	3.62	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Colon/Rectum														
All Drugs	111	98,449	1.13	----	---- - ----	----	---- - ----	181	317,199	0.57	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	39	37,315	1.05	0.89	0.60 - 1.31	0.96	0.65 - 1.43	60	91,931	0.65	1.22	0.89 - 1.66	1.26	0.92 - 1.72
Never exposed	72	61,134	1.18	Ref	---- - ----	----	---- - ----	121	225,268	0.54	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	58	35,872	1.62	1.91	1.32 - 2.77	1.82	1.26 - 2.65	70	130,717	0.54	0.90	0.67 - 1.21	0.88	0.65 - 1.18
Never exposed	53	62,577	0.85	Ref	---- - ----	----	---- - ----	111	186,481	0.60	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	16	20,084	0.80	0.66	0.39 - 1.12	0.63	0.37 - 1.07	36	73,017	0.49	0.83	0.58 - 1.20	0.84	0.58 - 1.21
Never exposed	95	78,364	1.21	Ref	---- - ----	----	---- - ----	145	244,181	0.59	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	9	10,502	0.86	0.74	0.37 - 1.46	0.68	0.34 - 1.35	25	36,272	0.69	1.24	0.81 - 1.89	1.15	0.75 - 1.75
Never exposed	102	87,947	1.16	Ref	---- - ----	----	---- - ----	156	280,926	0.56	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	3	1,707	1.76	1.57	0.50 - 4.96	1.51	0.48 - 4.75	3	5,440	0.55	0.97	0.31 - 3.02	0.90	0.29 - 2.80
Never exposed	108	96,742	1.12	Ref	---- - ----	----	---- - ----	178	311,758	0.57	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	3	5,335	0.56	0.48	0.15 - 1.53	0.42	0.13 - 1.34	11	14,171	0.78	1.38	0.75 - 2.55	1.25	0.68 - 2.31
Never exposed	108	93,114	1.16	Ref	---- - ----	----	---- - ----	170	303,027	0.56	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Kidney/Renal Pelvis														
All Drugs	86	98,444	0.87	----	---- - ----	----	---- - ----	84	317,368	0.26	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	34	37,306	0.91	1.07	0.70 - 1.65	1.14	0.74 - 1.76	34	91,993	0.37	1.67	1.08 - 2.58	1.72	1.11 - 2.66
Never exposed	52	61,138	0.85	Ref	---- - ----	----	---- - ----	50	225,375	0.22	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	32	35,879	0.89	1.03	0.67 - 1.60	1.00	0.64 - 1.55	29	130,786	0.22	0.75	0.48 - 1.18	0.75	0.48 - 1.18
Never exposed	54	62,564	0.86	Ref	---- - ----	----	---- - ----	55	186,582	0.29	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	13	20,083	0.65	0.69	0.39 - 1.25	0.67	0.37 - 1.20	13	73,063	0.18	0.61	0.34 - 1.11	0.60	0.33 - 1.08
Never exposed	73	78,360	0.93	Ref	---- - ----	----	---- - ----	71	244,306	0.29	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	7	10,495	0.67	0.74	0.34 - 1.61	0.70	0.32 - 1.51	13	36,305	0.36	1.42	0.78 - 2.56	1.34	0.74 - 2.42
Never exposed	79	87,949	0.90	Ref	---- - ----	----	---- - ----	71	281,064	0.25	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	2	1,707	1.17	1.35	0.33 - 5.48	1.29	0.32 - 5.26	2	5,443	0.37	1.40	0.34 - 5.68	1.29	0.32 - 5.26
Never exposed	84	96,737	0.87	Ref	---- - ----	----	---- - ----	82	311,925	0.26	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	3	5,323	0.56	0.63	0.20 - 2.00	0.58	0.18 - 1.84	3	14,172	0.21	0.79	0.25 - 2.51	0.74	0.23 - 2.36
Never exposed	83	93,121	0.89	Ref	---- - ----	----	---- - ----	81	303,196	0.27	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Lung/Bronchus														
All Drugs	128	98,480	1.30	----	---- - ----	----	---- - ----	223	317,268	0.70	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	38	37,344	1.02	0.69	0.47 - 1.01	0.78	0.54 - 1.15	66	91,951	0.72	1.03	0.77 - 1.37	1.07	0.80 - 1.42
Never exposed	90	61,136	1.47	Ref	---- - ----	----	---- - ----	157	225,317	0.70	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	51	35,877	1.42	1.16	0.81 - 1.65	1.08	0.76 - 1.54	99	130,722	0.76	1.14	0.87 - 1.48	1.12	0.86 - 1.46
Never exposed	77	62,603	1.23	Ref	---- - ----	----	---- - ----	124	186,545	0.66	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	33	20,078	1.64	1.36	0.91 - 2.02	1.26	0.85 - 1.87	48	73,030	0.66	0.92	0.67 - 1.26	0.92	0.67 - 1.26
Never exposed	95	78,402	1.21	Ref	---- - ----	----	---- - ----	175	244,238	0.72	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	11	10,505	1.05	0.79	0.42 - 1.46	0.70	0.38 - 1.30	29	36,309	0.80	1.16	0.78 - 1.71	1.07	0.72 - 1.57
Never exposed	117	87,975	1.33	Ref	---- - ----	----	---- - ----	194	280,959	0.69	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	4	1,707	2.34	1.83	0.68 - 4.95	1.66	0.61 - 4.48	5	5,440	0.92	1.31	0.54 - 3.19	1.20	0.50 - 2.92
Never exposed	124	96,773	1.28	Ref	---- - ----	----	---- - ----	218	311,828	0.70	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	4	5,333	0.75	0.56	0.21 - 1.52	0.48	0.18 - 1.31	8	14,177	0.56	0.80	0.39 - 1.61	0.72	0.36 - 1.46
Never exposed	124	93,148	1.33	Ref	---- - ----	----	---- - ----	215	303,091	0.71	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Melanoma														
All Drugs	38	98,548	0.39	----	---- - ----	----	---- - ----	59	317,383	0.19	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	14	37,348	0.37	0.96	0.49 - 1.85	1.04	0.54 - 2.01	20	91,986	0.22	1.26	0.73 - 2.15	1.27	0.74 - 2.18
Never exposed	24	61,200	0.39	Ref	---- - ----	----	---- - ----	39	225,397	0.17	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	17	35,923	0.47	1.41	0.74 - 2.67	1.35	0.71 - 2.55	30	130,770	0.23	1.48	0.89 - 2.46	1.47	0.88 - 2.45
Never exposed	21	62,625	0.34	Ref	---- - ----	----	---- - ----	29	186,613	0.16	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	11	20,095	0.55	1.59	0.79 - 3.21	1.53	0.76 - 3.08	13	73,060	0.18	0.95	0.51 - 1.75	0.94	0.51 - 1.75
Never exposed	27	78,452	0.34	Ref	---- - ----	----	---- - ----	46	244,323	0.19	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	4	10,508	0.38	0.99	0.35 - 2.78	0.91	0.32 - 2.57	3	36,330	0.08	0.41	0.13 - 1.32	0.40	0.12 - 1.27
Never exposed	34	88,039	0.39	Ref	---- - ----	----	---- - ----	56	281,053	0.20	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	1	1,710	0.58	1.53	0.21 - 11.16	1.44	0.20 - 10.52	0	5,445	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Never exposed	37	96,838	0.38	Ref	---- - ----	----	---- - ----	59	311,938	0.19	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	0	5,340	0.00	0.00	0.00 - ----	0.00	0.00 - .	3	14,179	0.21	1.15	0.36 - 3.66	1.10	0.34 - 3.52
Never exposed	38	93,208	0.41	Ref	---- - ----	----	---- - ----	56	303,203	0.18	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Non-hodgkin's Lymphoma														
All Drugs	101	98,420	1.03	----	---- - ----	----	---- - ----	163	317,201	0.51	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	39	37,296	1.05	1.03	0.69 - 1.54	1.11	0.74 - 1.66	50	91,956	0.54	1.08	0.78 - 1.51	1.11	0.80 - 1.55
Never exposed	62	61,124	1.01	Ref	---- - ----	----	---- - ----	113	225,245	0.50	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	41	35,870	1.14	1.19	0.80 - 1.77	1.14	0.77 - 1.70	63	130,704	0.48	0.90	0.66 - 1.23	0.90	0.65 - 1.23
Never exposed	60	62,550	0.96	Ref	---- - ----	----	---- - ----	100	186,498	0.54	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	21	20,070	1.05	1.02	0.63 - 1.66	0.99	0.61 - 1.60	34	73,020	0.47	0.88	0.60 - 1.29	0.87	0.60 - 1.27
Never exposed	80	78,350	1.02	Ref	---- - ----	----	---- - ----	129	244,181	0.53	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	10	10,487	0.95	0.92	0.48 - 1.77	0.86	0.45 - 1.65	17	36,280	0.47	0.90	0.55 - 1.49	0.84	0.51 - 1.40
Never exposed	91	87,934	1.03	Ref	---- - ----	----	---- - ----	146	280,921	0.52	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	3	1,708	1.76	1.73	0.55 - 5.47	1.66	0.53 - 5.24	4	5,436	0.74	1.44	0.53 - 3.89	1.33	0.49 - 3.59
Never exposed	98	96,713	1.01	Ref	---- - ----	----	---- - ----	159	311,765	0.51	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	2	5,339	0.37	0.35	0.09 - 1.43	0.32	0.08 - 1.28	11	14,161	0.78	1.55	0.84 - 2.86	1.43	0.78 - 2.64
Never exposed	99	93,082	1.06	Ref	---- - ----	----	---- - ----	152	303,040	0.50	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Pancreas														
All Drugs	32	98,560	0.32	----	---- - ----	----	---- - ----	53	317,480	0.17	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	14	37,361	0.37	1.27	0.63 - 2.56	1.38	0.68 - 2.77	10	92,038	0.11	0.57	0.29 - 1.13	0.59	0.30 - 1.18
Never exposed	18	61,199	0.29	Ref	---- - ----	----	---- - ----	43	225,442	0.19	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	13	35,920	0.36	1.19	0.59 - 2.42	1.15	0.57 - 2.32	26	130,828	0.20	1.37	0.80 - 2.35	1.35	0.79 - 2.31
Never exposed	19	62,640	0.30	Ref	---- - ----	----	---- - ----	27	186,652	0.14	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	4	20,101	0.20	0.56	0.20 - 1.59	0.53	0.19 - 1.51	11	73,077	0.15	0.88	0.45 - 1.70	0.88	0.45 - 1.70
Never exposed	28	78,459	0.36	Ref	---- - ----	----	---- - ----	42	244,404	0.17	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	3	10,509	0.29	0.87	0.26 - 2.85	0.80	0.24 - 2.64	9	36,326	0.25	1.58	0.77 - 3.24	1.46	0.71 - 2.99
Never exposed	29	88,051	0.33	Ref	---- - ----	----	---- - ----	44	281,154	0.16	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	0	1,711	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	5,444	0.37	2.25	0.55 - 9.23	2.04	0.50 - 8.40
Never exposed	32	96,849	0.33	Ref	---- - ----	----	---- - ----	51	312,036	0.16	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	2	5,337	0.37	1.16	0.28 - 4.87	1.06	0.25 - 4.46	1	14,186	0.07	0.41	0.06 - 2.97	0.37	0.05 - 2.68
Never exposed	30	93,222	0.32	Ref	---- - ----	----	---- - ----	52	303,294	0.17	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Prostate (Men only)														
All Drugs	1,428	95,646	14.93	----	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Oxybutynin								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	531	36,177	14.68	0.97	0.87 - 1.08	1.07	0.96 - 1.19	----	----	----	----	---- - ----	----	---- - ----
Never exposed	897	59,469	15.08	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Tolterodine								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	465	34,773	13.37	0.85	0.76 - 0.94	0.80	0.72 - 0.90	----	----	----	----	---- - ----	----	---- - ----
Never exposed	963	60,873	15.82	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Solifenacin								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	278	19,482	14.27	0.95	0.83 - 1.08	0.89	0.78 - 1.01	----	----	----	----	---- - ----	----	---- - ----
Never exposed	1,150	76,165	15.10	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Darifenacin								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	146	10,142	14.40	0.96	0.81 - 1.14	0.88	0.74 - 1.04	----	----	----	----	---- - ----	----	---- - ----
Never exposed	1,282	85,504	14.99	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Fesoterodine								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	27	1,648	16.39	1.10	0.75 - 1.61	1.02	0.70 - 1.50	----	----	----	----	---- - ----	----	---- - ----
Never exposed	1,401	93,999	14.90	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Trospium								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	83	5,117	16.22	1.09	0.87 - 1.36	0.97	0.78 - 1.21	----	----	----	----	---- - ----	----	---- - ----
Never exposed	1,345	90,530	14.86	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Optum Research Database: 01 January 2004 - 30 September 2012

	Men						Women					
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	95% CI
Uterus (Women only)														
All Drugs	----	----	----	----	---- - ----	----	---- - ----	108	317,360	0.34	----	---- - ----	----	---- - ----
Oxybutynin	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	32	91,996	0.35	1.03	0.68 - 1.56	1.06	0.70 - 1.61
Never exposed	----	----	----	----	---- - ----	----	---- - ----	76	225,364	0.34	Ref	---- - ----	----	---- - ----
Tolterodine	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	51	130,766	0.39	1.28	0.88 - 1.86	1.28	0.88 - 1.87
Never exposed	----	----	----	----	---- - ----	----	---- - ----	57	186,594	0.31	Ref	---- - ----	----	---- - ----
Solifenacin	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	21	73,058	0.29	0.81	0.50 - 1.30	0.79	0.49 - 1.27
Never exposed	----	----	----	----	---- - ----	----	---- - ----	87	244,302	0.36	Ref	---- - ----	----	---- - ----
Darifenacin	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	10	36,307	0.28	0.79	0.41 - 1.51	0.74	0.39 - 1.42
Never exposed	----	----	----	----	---- - ----	----	---- - ----	98	281,053	0.35	Ref	---- - ----	----	---- - ----
Fesoterodine	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	2	5,444	0.37	1.08	0.27 - 4.38	1.00	0.25 - 4.04
Never exposed	----	----	----	----	---- - ----	----	---- - ----	106	311,917	0.34	Ref	---- - ----	----	---- - ----
Trospium	----	----	----	----	---- - ----	----	---- - ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	2	14,181	0.14	0.40	0.10 - 1.63	0.38	0.09 - 1.53
Never exposed	----	----	----	----	---- - ----	----	---- - ----	106	303,180	0.35	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men						Women					
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR [‖,¶]
Any of Top 10 Cancers												
All Drugs	1,133	28,269	40.08	----	---- - ----	----	790	57,663	13.70	----	---- - ----	----
Oxybutynin												
Ever exposed	412	9,309	44.26	1.16	1.03 - 1.31	1.16	252	15,925	15.82	1.23	1.06 - 1.43	1.23
Never exposed	721	18,960	38.03	Ref	---- - ----	----	538	41,738	12.89	Ref	---- - ----	----
Tolterodine												
Ever exposed	406	10,992	36.94	0.88	0.78 - 0.99	0.88	311	24,779	12.55	0.86	0.75 - 0.99	0.86
Never exposed	727	17,277	42.08	Ref	---- - ----	----	479	32,884	14.57	Ref	---- - ----	----
Solifenacin												
Ever exposed	222	6,164	36.01	0.87	0.75 - 1.01	0.87	152	12,616	12.05	0.85	0.71 - 1.02	0.85
Never exposed	911	22,104	41.21	Ref	---- - ----	----	638	45,047	14.16	Ref	---- - ----	----
Darifenacin												
Ever exposed	123	3,490	35.24	0.86	0.72 - 1.04	0.86	112	7,308	15.33	1.14	0.93 - 1.39	1.14
Never exposed	1,010	24,779	40.76	Ref	---- - ----	----	678	50,356	13.46	Ref	---- - ----	----
Fesoterodine												
Ever exposed	23	536	42.94	1.07	0.71 - 1.62	1.07	17	1,126	15.10	1.10	0.68 - 1.79	1.10
Never exposed	1,110	27,733	40.02	Ref	---- - ----	----	773	56,537	13.67	Ref	---- - ----	----
Trospium												
Ever exposed	53	1,995	26.56	0.65	0.49 - 0.85	0.65	38	3,140	12.10	0.88	0.63 - 1.22	0.88
Never exposed	1,080	26,274	41.11	Ref	---- - ----	----	752	54,523	13.79	Ref	---- - ----	----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Bladder														
All Drugs	200	30,116	6.64	----	---- - ----	----	---- - ----	96	58,935	1.63	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	101	9,974	10.13	2.06	1.56 - 2.72	2.08	1.58 - 2.74	43	16,311	2.64	2.12	1.42 - 3.17	2.12	1.42 - 3.18
Never exposed	99	20,142	4.92	Ref	---- - ----	----	---- - ----	53	42,624	1.24	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	57	11,789	4.83	0.62	0.46 - 0.84	0.61	0.45 - 0.84	27	25,353	1.06	0.52	0.33 - 0.81	0.52	0.33 - 0.81
Never exposed	143	18,326	7.80	Ref	---- - ----	----	---- - ----	69	33,582	2.05	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	33	6,612	4.99	0.70	0.48 - 1.02	0.71	0.49 - 1.02	15	12,899	1.16	0.66	0.38 - 1.15	0.66	0.38 - 1.14
Never exposed	167	23,503	7.11	Ref	---- - ----	----	---- - ----	81	46,036	1.76	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	12	3,750	3.20	0.45	0.25 - 0.80	0.45	0.25 - 0.80	12	7,532	1.59	0.97	0.53 - 1.79	0.98	0.53 - 1.79
Never exposed	188	26,366	7.13	Ref	---- - ----	----	---- - ----	84	51,403	1.63	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	4	583	6.86	1.03	0.38 - 2.78	1.04	0.39 - 2.79	2	1,157	1.73	1.06	0.26 - 4.31	1.06	0.26 - 4.29
Never exposed	196	29,532	6.64	Ref	---- - ----	----	---- - ----	94	57,777	1.63	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	8	2,133	3.75	0.55	0.27 - 1.11	0.53	0.26 - 1.08	5	3,225	1.55	0.95	0.39 - 2.33	0.95	0.39 - 2.34
Never exposed	192	27,982	6.86	Ref	---- - ----	----	---- - ----	91	55,710	1.63	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Breast (Women only)														
All Drugs	----	----	----	----	---- - ----	----	---- - ----	334	58,400	5.72	----	---- - ----	----	---- - ----
Oxybutynin	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	88	16,178	5.44	0.93	0.73 - 1.19	0.93	0.73 - 1.19
Never exposed	----	----	----	----	---- - ----	----	---- - ----	246	42,222	5.83	Ref	---- - ----	----	---- - ----
Tolterodine	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	138	25,086	5.50	0.94	0.75 - 1.16	0.94	0.75 - 1.16
Never exposed	----	----	----	----	---- - ----	----	---- - ----	196	33,315	5.88	Ref	---- - ----	----	---- - ----
Solifenacin	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	70	12,758	5.49	0.95	0.73 - 1.23	0.95	0.73 - 1.23
Never exposed	----	----	----	----	---- - ----	----	---- - ----	264	45,642	5.78	Ref	---- - ----	----	---- - ----
Darifenacin	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	43	7,458	5.77	1.01	0.73 - 1.39	1.01	0.73 - 1.39
Never exposed	----	----	----	----	---- - ----	----	---- - ----	291	50,943	5.71	Ref	---- - ----	----	---- - ----
Fesoterodine	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	7	1,144	6.12	1.07	0.51 - 2.26	1.07	0.51 - 2.26
Never exposed	----	----	----	----	---- - ----	----	---- - ----	327	57,256	5.71	Ref	---- - ----	----	---- - ----
Trospium	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	17	3,189	5.33	0.93	0.57 - 1.51	0.93	0.57 - 1.51
Never exposed	----	----	----	----	---- - ----	----	---- - ----	317	55,211	5.74	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI
Colon/Rectum														
All Drugs	56	30,413	1.84	----	---- - ----	----	---- - ----	87	58,938	1.48	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	18	10,159	1.77	0.94	0.54 - 1.65	0.95	0.54 - 1.67	29	16,312	1.78	1.31	0.84 - 2.04	1.30	0.83 - 2.03
Never exposed	38	20,254	1.88	Ref	---- - ----	----	---- - ----	58	42,626	1.36	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	34	11,857	2.87	2.42	1.41 - 4.13	2.40	1.40 - 4.10	32	25,348	1.26	0.77	0.50 - 1.19	0.76	0.49 - 1.18
Never exposed	22	18,556	1.19	Ref	---- - ----	----	---- - ----	55	33,590	1.64	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	8	6,666	1.20	0.59	0.28 - 1.26	0.60	0.28 - 1.26	15	12,910	1.16	0.74	0.43 - 1.30	0.75	0.43 - 1.32
Never exposed	48	23,747	2.02	Ref	---- - ----	----	---- - ----	72	46,028	1.56	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	7	3,771	1.86	1.01	0.46 - 2.23	1.00	0.45 - 2.20	13	7,523	1.73	1.20	0.67 - 2.16	1.19	0.66 - 2.15
Never exposed	49	26,641	1.84	Ref	---- - ----	----	---- - ----	74	51,415	1.44	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	3	589	5.09	2.86	0.90 - 9.17	2.87	0.90 - 9.20	2	1,157	1.73	1.17	0.29 - 4.77	1.19	0.29 - 4.82
Never exposed	53	29,823	1.78	Ref	---- - ----	----	---- - ----	85	57,781	1.47	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	2	2,145	0.93	0.49	0.12 - 2.00	0.47	0.11 - 1.93	4	3,232	1.24	0.83	0.30 - 2.27	0.83	0.30 - 2.25
Never exposed	54	28,268	1.91	Ref	---- - ----	----	---- - ----	83	55,706	1.49	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[||] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Kidney/Renal Pelvis														
All Drugs	34	30,416	1.12	----	---- - ----	----	---- - ----	31	59,027	0.53	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	15	10,141	1.48	1.58	0.80 - 3.11	1.58	0.80 - 3.11	11	16,347	0.67	1.44	0.69 - 3.00	1.45	0.69 - 3.02
Never exposed	19	20,275	0.94	Ref	---- - ----	----	---- - ----	20	42,680	0.47	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	9	11,876	0.76	0.56	0.26 - 1.20	0.56	0.26 - 1.20	11	25,382	0.43	0.73	0.35 - 1.52	0.75	0.36 - 1.56
Never exposed	25	18,540	1.35	Ref	---- - ----	----	---- - ----	20	33,645	0.59	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	9	6,658	1.35	1.28	0.60 - 2.75	1.29	0.60 - 2.75	4	12,920	0.31	0.53	0.19 - 1.51	0.51	0.18 - 1.47
Never exposed	25	23,758	1.05	Ref	---- - ----	----	---- - ----	27	46,107	0.59	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	4	3,767	1.06	0.94	0.33 - 2.68	0.94	0.33 - 2.67	7	7,541	0.93	1.99	0.86 - 4.62	2.02	0.87 - 4.69
Never exposed	30	26,649	1.13	Ref	---- - ----	----	---- - ----	24	51,486	0.47	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	1	590	1.69	1.53	0.21 - 11.20	1.53	0.21 - 11.20	0	1,161	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Never exposed	33	29,826	1.11	Ref	---- - ----	----	---- - ----	31	57,866	0.54	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	2	2,137	0.94	0.83	0.20 - 3.45	0.82	0.20 - 3.44	1	3,227	0.31	0.58	0.08 - 4.23	0.58	0.08 - 4.28
Never exposed	32	28,279	1.13	Ref	---- - ----	----	---- - ----	30	55,800	0.54	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI
Lung/Bronchus														
All Drugs	87	30,404	2.86	----	---- - ----	----	---- - ----	102	58,976	1.73	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	23	10,168	2.26	0.72	0.44 - 1.15	0.71	0.44 - 1.14	34	16,323	2.08	1.31	0.87 - 1.97	1.30	0.86 - 1.97
Never exposed	64	20,236	3.16	Ref	---- - ----	----	---- - ----	68	42,653	1.59	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	31	11,857	2.61	0.87	0.56 - 1.34	0.88	0.56 - 1.36	47	25,343	1.85	1.13	0.77 - 1.67	1.12	0.76 - 1.66
Never exposed	56	18,547	3.02	Ref	---- - ----	----	---- - ----	55	33,632	1.64	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	27	6,657	4.06	1.61	1.02 - 2.53	1.60	1.01 - 2.51	21	12,899	1.63	0.93	0.57 - 1.50	0.94	0.58 - 1.52
Never exposed	60	23,748	2.53	Ref	---- - ----	----	---- - ----	81	46,076	1.76	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	11	3,772	2.92	1.02	0.54 - 1.92	1.03	0.55 - 1.95	15	7,545	1.99	1.18	0.68 - 2.03	1.17	0.68 - 2.02
Never exposed	76	26,632	2.85	Ref	---- - ----	----	---- - ----	87	51,430	1.69	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	2	591	3.39	1.19	0.29 - 4.83	1.18	0.29 - 4.80	3	1,159	2.59	1.51	0.48 - 4.77	1.52	0.48 - 4.80
Never exposed	85	29,813	2.85	Ref	---- - ----	----	---- - ----	99	57,816	1.71	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	3	2,143	1.40	0.47	0.15 - 1.49	0.49	0.15 - 1.55	4	3,230	1.24	0.70	0.26 - 1.91	0.70	0.26 - 1.90
Never exposed	84	28,262	2.97	Ref	---- - ----	----	---- - ----	98	55,745	1.76	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[||] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI
Melanoma														
All Drugs	20	30,462	0.66	----	---- - ----	----	---- - ----	16	59,056	0.27	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	5	10,179	0.49	0.66	0.24 - 1.83	0.67	0.24 - 1.84	5	16,352	0.31	1.19	0.41 - 3.42	1.18	0.41 - 3.39
Never exposed	15	20,283	0.74	Ref	---- - ----	----	---- - ----	11	42,704	0.26	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	9	11,887	0.76	1.28	0.53 - 3.09	1.27	0.53 - 3.07	6	25,393	0.24	0.80	0.29 - 2.19	0.78	0.28 - 2.14
Never exposed	11	18,575	0.59	Ref	---- - ----	----	---- - ----	10	33,663	0.30	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	8	6,669	1.20	2.38	0.97 - 5.82	2.39	0.98 - 5.84	5	12,920	0.39	1.62	0.56 - 4.67	1.67	0.58 - 4.81
Never exposed	12	23,793	0.50	Ref	---- - ----	----	---- - ----	11	46,136	0.24	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	2	3,776	0.53	0.79	0.18 - 3.38	0.78	0.18 - 3.36	2	7,556	0.26	0.97	0.22 - 4.28	0.96	0.22 - 4.23
Never exposed	18	26,685	0.67	Ref	---- - ----	----	---- - ----	14	51,500	0.27	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	0	593	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0	1,162	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Never exposed	20	29,869	0.67	Ref	---- - ----	----	---- - ----	16	57,894	0.28	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	0	2,149	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	3,232	0.62	2.47	0.56 - 10.86	2.44	0.55 - 10.73
Never exposed	20	28,313	0.71	Ref	---- - ----	----	---- - ----	14	55,824	0.25	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[||] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Non-hodgkin's Lymphoma														
All Drugs	47	30,397	1.55	----	---- - ----	----	---- - ----	64	58,948	1.09	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	15	10,158	1.48	0.93	0.51 - 1.72	0.94	0.51 - 1.74	24	16,315	1.47	1.57	0.95 - 2.60	1.57	0.95 - 2.60
Never exposed	32	20,239	1.58	Ref	---- - ----	----	---- - ----	40	42,633	0.94	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	23	11,849	1.94	1.50	0.85 - 2.66	1.49	0.84 - 2.64	25	25,334	0.99	0.85	0.51 - 1.41	0.85	0.52 - 1.41
Never exposed	24	18,548	1.29	Ref	---- - ----	----	---- - ----	39	33,614	1.16	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	11	6,656	1.65	1.09	0.55 - 2.14	1.09	0.56 - 2.15	8	12,902	0.62	0.51	0.24 - 1.07	0.51	0.24 - 1.07
Never exposed	36	23,741	1.52	Ref	---- - ----	----	---- - ----	56	46,047	1.22	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	3	3,769	0.80	0.48	0.15 - 1.55	0.48	0.15 - 1.54	8	7,530	1.06	0.98	0.47 - 2.05	0.98	0.47 - 2.05
Never exposed	44	26,628	1.65	Ref	---- - ----	----	---- - ----	56	51,419	1.09	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	2	590	3.39	2.24	0.54 - 9.25	2.25	0.55 - 9.28	2	1,155	1.73	1.61	0.39 - 6.60	1.61	0.39 - 6.59
Never exposed	45	29,807	1.51	Ref	---- - ----	----	---- - ----	62	57,793	1.07	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	1	2,149	0.47	0.29	0.04 - 2.07	0.28	0.04 - 2.02	3	3,226	0.93	0.85	0.27 - 2.71	0.85	0.27 - 2.71
Never exposed	46	28,248	1.63	Ref	---- - ----	----	---- - ----	61	55,722	1.09	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI
Pancreas														
All Drugs	15	30,464	0.49	----	---- - ----	----	---- - ----	27	59,066	0.46	----	---- - ----	----	---- - ----
Oxybutynin														
Ever exposed	8	10,179	0.79	2.28	0.83 - 6.28	2.26	0.82 - 6.23	6	16,361	0.37	0.75	0.30 - 1.85	0.75	0.30 - 1.85
Never exposed	7	20,285	0.35	Ref	---- - ----	----	---- - ----	21	42,705	0.49	Ref	---- - ----	----	---- - ----
Tolterodine														
Ever exposed	6	11,882	0.50	1.04	0.37 - 2.93	1.05	0.37 - 2.95	10	25,395	0.39	0.78	0.36 - 1.70	0.78	0.36 - 1.71
Never exposed	9	18,582	0.48	Ref	---- - ----	----	---- - ----	17	33,670	0.50	Ref	---- - ----	----	---- - ----
Solifenacin														
Ever exposed	2	6,677	0.30	0.55	0.12 - 2.43	0.55	0.12 - 2.42	7	12,923	0.54	1.25	0.53 - 2.96	1.24	0.53 - 2.94
Never exposed	13	23,787	0.55	Ref	---- - ----	----	---- - ----	20	46,142	0.43	Ref	---- - ----	----	---- - ----
Darifenacin														
Ever exposed	0	3,778	0.00	0.00	0.00 - ----	0.00	0.00 - ----	6	7,550	0.79	1.95	0.79 - 4.83	1.95	0.79 - 4.84
Never exposed	15	26,686	0.56	Ref	---- - ----	----	---- - ----	21	51,515	0.41	Ref	---- - ----	----	---- - ----
Fesoterodine														
Ever exposed	0	593	0.00	0.00	0.00 - ----	0.00	0.00 - ----	2	1,161	1.72	3.99	0.94 - 16.84	3.98	0.94 - 16.80
Never exposed	15	29,871	0.50	Ref	---- - ----	----	---- - ----	25	57,904	0.43	Ref	---- - ----	----	---- - ----
Trospium														
Ever exposed	0	2,149	0.00	0.00	0.00 - ----	0.00	0.00 - ----	0	3,236	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Never exposed	15	28,315	0.53	Ref	---- - ----	----	---- - ----	27	55,829	0.48	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[||] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men							Women						
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[,¶]	95% CI
Prostate (Men only)														
All Drugs	683	28,987	23.56	----	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Oxybutynin								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	231	9,638	23.97	1.03	0.88 - 1.20	1.02	0.87 - 1.20	----	----	----	----	---- - ----	----	---- - ----
Never exposed	452	19,349	23.36	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Tolterodine								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	239	11,271	21.21	0.85	0.72 - 0.99	0.85	0.72 - 0.99	----	----	----	----	---- - ----	----	---- - ----
Never exposed	444	17,716	25.06	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Solifenacin								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	127	6,340	20.03	0.82	0.67 - 0.99	0.82	0.67 - 0.99	----	----	----	----	---- - ----	----	---- - ----
Never exposed	556	22,647	24.55	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Darifenacin								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	84	3,555	23.63	1.00	0.80 - 1.26	1.01	0.80 - 1.26	----	----	----	----	---- - ----	----	---- - ----
Never exposed	599	25,432	23.55	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Fesoterodine								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	11	556	19.79	0.84	0.46 - 1.52	0.84	0.46 - 1.52	----	----	----	----	---- - ----	----	---- - ----
Never exposed	672	28,431	23.64	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----
Trospium								----	----	----	----	---- - ----	----	---- - ----
Ever exposed	38	2,032	18.70	0.78	0.56 - 1.08	0.79	0.57 - 1.09	----	----	----	----	---- - ----	----	---- - ----
Never exposed	645	26,955	23.93	Ref	---- - ----	----	---- - ----	----	----	----	----	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[||] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table C4.1. Crude and Adjusted Association between Antimuscarinic Drugs and First Claims-Identified Cancer Outcomes after Cohort Entry (Index drug use), Based on "Ever Exposed Person-time", Among Patients ≥ 65 Years at Index Date, Optum Research Database: 01 January 2004 - 30 September 2012*

	Men						Women					
	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI	No. of cases[†]	Person-Years[‡]	IR[§]	Crude IRR	95% CI	Adjusted IRR[‖,¶]	95% CI
Uterus (Women only)														
All Drugs	----	----	----	----	---- - ----	----	---- - ----	38	59,030	0.64	----	---- - ----	----	---- - ----
Oxybutynin	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	12	16,349	0.73	1.20	0.61 - 2.39	1.21	0.61 - 2.39
Never exposed	----	----	----	----	---- - ----	----	---- - ----	26	42,681	0.61	Ref	---- - ----	----	---- - ----
Tolterodine	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	18	25,381	0.71	1.19	0.63 - 2.26	1.20	0.63 - 2.27
Never exposed	----	----	----	----	---- - ----	----	---- - ----	20	33,649	0.59	Ref	---- - ----	----	---- - ----
Solifenacin	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	8	12,915	0.62	0.95	0.44 - 2.08	0.95	0.43 - 2.07
Never exposed	----	----	----	----	---- - ----	----	---- - ----	30	46,115	0.65	Ref	---- - ----	----	---- - ----
Darifenacin	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	6	7,540	0.80	1.28	0.54 - 3.06	1.28	0.54 - 3.07
Never exposed	----	----	----	----	---- - ----	----	---- - ----	32	51,489	0.62	Ref	---- - ----	----	---- - ----
Fesoterodine	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	0	1,162	0.00	0.00	0.00 - ----	0.00	0.00 - ----
Never exposed	----	----	----	----	---- - ----	----	---- - ----	38	57,868	0.66	Ref	---- - ----	----	---- - ----
Trospium	----	----	----	----	---- ----	----	---- ----							
Ever exposed	----	----	----	----	---- - ----	----	---- - ----	2	3,231	0.62	0.96	0.23 - 3.98	0.96	0.23 - 3.99
Never exposed	----	----	----	----	---- - ----	----	---- - ----	36	55,798	0.65	Ref	---- - ----	----	---- - ----

Abbreviations: CI, Confidence Interval; IR, Incidence Rate; IRR, Incidence Rate Ratio; Ref, Referent Category

[†] Includes only patients who do not meet the definition for baseline cancer.

[‡] Follow-up time for all users of the 6 study drugs begins on the day after they are dispensed the study drug. Follow-up ends on the earliest of the following: disenrollment from the health plan, dispensing of a different Antimuscarinic medication, death or end of study period.

[§] IR: Incidence Rate per 1,000 person-years

[‖] Referent category is unexposed person-time.

[¶] Adjusted for age group at baseline, using Poisson regression analysis

Table D1a. Comparison of Claims-Identified Baseline Patient Characteristics (Categorical) Across Antimuscarinic Index Treatment Groups Based on Drug Approval Date Before/After 2004, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Oxybutynin/Tolterodine N = 133,603		Solifenacin/Darifenacin/ Fesoterodine/Trospium N = 71,820	
	N	%	N	%
Prescriber Category				
Urology	36,481	27.3	25,280	35.2
Family/General Practice	44,023	33.0	18,733	26.1
OB/GYN	17,483	13.1	11,660	16.2
Miscellaneous / Unknown	35,616	26.7	16,147	22.5
Age				
18-44	32,068	24.0	15,128	21.1
45-54	34,311	25.7	18,545	25.8
55-64	38,935	29.1	22,644	31.5
65-74	15,044	11.3	8,410	11.7
75+	13,245	9.9	7,093	9.9
Gender				
Female	96,296	72.1	53,842	75.0
Male	37,307	27.9	17,978	25.0
Region				
Midwest	31,322	23.4	15,788	22.0
Northeast	12,299	9.2	5,539	7.7
South	69,566	52.1	41,514	57.8
West	20,416	15.3	8,979	12.5
Year of Cohort Entry				
2004	22,269	16.7	305	0.4
2005	19,213	14.4	4,719	6.6
2006	18,450	13.8	8,884	12.4
2007	15,617	11.7	9,192	12.8
2008	17,238	12.9	10,825	15.1
2009	14,481	10.8	10,692	14.9
2010	10,124	7.6	10,704	14.9
2011	9,443	7.1	9,951	13.9
2012	6,768	5.1	6,548	9.1
Incontinence				
Yes	24,626	18.4	20,713	28.8
No	108,977	81.6	51,107	71.2
Overactive Bladder				
Yes	7,969	6.0	8,088	11.3
No	125,634	94.0	63,732	88.7
Cardiovascular Disease				
Yes	9,577	7.2	5,112	7.1
No	124,026	92.8	66,708	92.9

* Baseline period began July 1, 2003.

Table D1a. Comparison of Claims-Identified Baseline Patient Characteristics (Categorical) Across Antimuscarinic Index Treatment Groups Based on Drug Approval Date Before/After 2004, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Oxybutynin/Tolterodine N = 133,603		Solifenacin/Darifenacin/ Fesoterodine/Trospium N = 71,820	
	N	%	N	%
Cerebrovascular Disease				
Yes	1,607	1.2	726	1.0
No	131,996	98.8	71,094	99.0
Coronary Artery Disease				
Yes	7,641	5.7	4,239	5.9
No	125,962	94.3	67,581	94.1
Angina				
Yes	1,083	0.8	543	0.8
No	132,520	99.2	71,277	99.2
Congestive Heart Failure				
Yes	2,717	2.0	1,235	1.7
No	130,886	98.0	70,585	98.3
Atrial Fibrillation				
Yes	3,196	2.4	1,740	2.4
No	130,407	97.6	70,080	97.6
Antiarrhythmic Medications				
Yes	24,841	18.6	13,488	18.8
No	108,762	81.4	58,332	81.2
Hypertension				
Yes	42,936	32.1	24,188	33.7
No	90,667	67.9	47,632	66.3
Antihypertensives				
Yes	56,433	42.2	31,128	43.3
No	77,170	57.8	40,692	56.7
Diabetes				
Yes	11,727	8.8	6,655	9.3
No	121,876	91.2	65,165	90.7
High CV Risk Composite				
Yes	63,905	47.8	35,215	49.0
No	69,698	52.2	36,605	51.0
Hyperlipidemia				
Yes	42,735	32.0	24,384	34.0
No	90,868	68.0	47,436	66.1
Ischemic Heart Disease, excluding AMI				
Yes	8,380	6.3	4,616	6.4
No	125,223	93.7	67,204	93.6
Acute Myocardial Infarction				
Yes	339	0.3	144	0.2
No	133,264	99.8	71,676	99.8

Abbreviations: AMI, Acute Myocardial Infarction; CV, Cardiovascular Disease

* Baseline period began July 1, 2003.

Table D1a. Comparison of Claims-Identified Baseline Patient Characteristics (Categorical) Across Antimuscarinic Index Treatment Groups Based on Drug Approval Date Before/After 2004, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Oxybutynin/Tolterodine N = 133,603		Solifenacin/Darifenacin/ Fesoterodine/Trospium N = 71,820	
	N	%	N	%
Stroke				
Yes	809	0.6	318	0.4
No	132,794	99.4	71,502	99.6
Hypertriglyceridemia				
Yes	871	0.7	503	0.7
No	132,732	99.4	71,317	99.3
Organ Transplant				
Yes	740	0.6	207	0.3
No	132,863	99.5	71,613	99.7
Alcohol Use / Abuse				
Yes	678	0.5	293	0.4
No	132,925	99.5	71,527	99.6
Smoking				
Yes	4,305	3.2	1,897	2.6
No	129,298	96.8	69,923	97.4
Overweight / Obesity				
Yes	5,754	4.3	3,324	4.6
No	127,849	95.7	68,496	95.4
Gout				
Yes	1,138	0.9	588	0.8
No	132,465	99.2	71,232	99.2
Rheumatoid Arthritis				
Yes	1,814	1.4	1,172	1.6
No	131,789	98.6	70,648	98.4
Dementia				
Yes	530	0.4	276	0.4
No	133,073	99.6	71,544	99.6
Peptic Ulcer Disease				
Yes	607	0.5	294	0.4
No	132,996	99.6	71,526	99.6
Chronic Obstructive Pulmonary Disease				
Yes	3,602	2.7	1,842	2.6
No	130,001	97.3	69,978	97.4
Renal Impairment / Dialysis				
Yes	3,830	2.9	1,797	2.5
No	129,773	97.1	70,023	97.5

* Baseline period began July 1, 2003.

Table D1a. Comparison of Claims-Identified Baseline Patient Characteristics (Categorical) Across Antimuscarinic Index Treatment Groups Based on Drug Approval Date Before/After 2004, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Oxybutynin/Tolterodine N = 133,603		Solifenacin/Darifenacin/ Fesoterodine/Trospium N = 71,820	
	N	%	N	%
Open Heart Surgeries				
Yes	560	0.4	271	0.4
No	133,043	99.6	71,549	99.6
Hospitalization within 45 Days of Cohort Entry Date				
Yes	8,628	6.5	1,224	1.7
No	124,975	93.5	70,596	98.3
Cholesterol Lowering Therapies				
Yes	35,707	26.7	21,940	30.6
No	97,896	73.3	49,880	69.5
Any CV Drug				
Yes	67,380	50.4	37,993	52.9
No	66,223	49.6	33,827	47.1
Any History of Cancer				
Yes	9,406	7.0	4,340	6.0
No	124,197	93.0	67,480	94.0
Endometrial Polyps (women only)				
Yes	175	0.2	108	0.2
No	96,121	99.8	53,734	99.8
Irritable Bowel Syndrome				
Yes	2,461	1.8	1,383	1.9
No	131,142	98.2	70,437	98.1
Polycystic Ovary Syndrome (women only)				
Yes	248	0.3	157	0.3
No	96,048	99.7	53,685	99.7
Any Cancer Drug				
Yes	6,407	4.8	3,460	4.8
No	127,196	95.2	68,360	95.2
Alkylating Agents				
Yes	143	0.1	32	0.0
No	133,460	99.9	71,788	100
Antimetabolites				
Yes	1,511	1.1	907	1.3
No	132,092	98.9	70,913	98.7
Antimicrotubule Agents				
Yes	0	0.0	0	0.0
No	133,603	100	71,820	100

Abbreviations: CV, Cardiovascular Disease

* Baseline period began July 1, 2003.

Table D1a. Comparison of Claims-Identified Baseline Patient Characteristics (Categorical) Across Antimuscarinic Index Treatment Groups Based on Drug Approval Date Before/After 2004, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Oxybutynin/Tolterodine N = 133,603		Solifenacin/Darifenacin/ Fesoterodine/Trospium N = 71,820	
	N	%	N	%
Topoisomerase-active Agents				
Yes	12	0.0	4	0.0
No	133,591	100	71,816	100
Antineoplastic Antibiotics				
Yes	0	0.0	0	0.0
No	133,603	100	71,820	100
Endocrine Agents				
Yes	4,669	3.5	2,515	3.5
No	128,934	96.5	69,305	96.5
Biologically-directed Therapies				
Yes	122	0.1	51	0.1
No	133,481	99.9	71,769	99.9
Immune Therapies				
Yes	69	0.1	19	0.0
No	133,534	100	71,801	100
Miscellaneous Agents				
Yes	7	0.0	5	0.0
No	133,596	100	71,815	100

* Baseline period began July 1, 2003.

Table D1b. Comparison of Claims-Identified Baseline Patient Characteristics (Continuous) Across Antimuscarinic Index Treatment Groups Based on Drug Approval Date Before/After 2004, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline* Patient Characteristics	Index drug: Oxybutynin/ Tolterodine N = 133,603				Index drug: Solifenacin/ Darifenacin/ Fesoterodine/ Trospium N = 71,820			
	Median	IQR	Mean	SD	Median	IQR	Mean	SD
Membership† Length (Months)	29	(15 - 50)	36.5	28.7	30	(15 - 56)	40.0	31.7
Number of Days in Hospital During Baseline (Entire Cohort)	0	(0 - 0)	1.4	7.8	0	(0 - 0)	0.8	5.7
Number of Days in Hospital During Baseline (Among Patients with at least 1 Day) (N=28,629)	3	(2 - 6)	8.7	17.8	3	(2 - 6)	7.8	16.2
Total Health Care Costs ($)	2,954	(1,179 - 8,195)	9,074.9	27,011.6	3,094	(1,437 - 7,093)	7,304.9	18,101.3
Total Drug Costs ($)	664	(248 - 1,552)	1,344.3	2,381.8	874	(362 - 1,908)	1,624.8	2,580.1
Number of Unique ICD-9 DX Codes in Baseline (3-Digit Level)	27	(16 - 44)	32.4	22.7	26	(16 - 42)	31.3	21.3
Number of Unique Drugs Dispensed in Baseline (HICL Level)	7	(4 - 11)	8.1	5.2	7	(4 - 11)	8.4	5.3
Number of Unique Laboratory Tests in Baseline	11	(5 - 21)	15.5	14.9	11	(5 - 21)	15.3	14.1

Abbreviations: HICL, Hierarchical Ingredient Code List; IQR, Interquartile Range; SD, Standard Deviation

* Baseline period began July 1, 2003.

† Membership starting at health plan enrollment through index date

Table D2. Pattern of Drug Dispensings, Optum Research Database: 01 January 2004 - 30 September 2012

Drugs Dispensed During Study Period														
	Oxybutynin		**Tolterodine**		**Solifenacin**		**Darifenacin**		**Fesoterodine**		**Trospium**		**Total**	
Number of Index Users	N = 66,502		N = 67,101		N = 43,162		N = 17,945		N = 3,963		N = 6,750		N = 205,423	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Number of Patients Who Used Only Index Drug	57,816	86.9%	52,024	77.5%	36,718	85.1%	14,191	79.1%	5,849	86.7%	2,185	55.1%	168,783	82.2%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Number of Dispensings (Index drug only)	1	(1,4)	2	(1 - 4)	2	(1 - 7)	2	(1 - 6)	2	(1 - 4)	2	(1 - 5)	--	--
Number of Dispensings (All drugs)	**2**	(1 -5)	2	(1 - 7)	3	(1 - 8)	3	(1 - 9)	2	(1 - 6)	3	(1 - 8)	2	(1-7)

Second Drug Dispensed During Study Period														
Index Drug	**Oxybutynin**		**Tolterodine**		**Solifenacin**		**Darifenacin**		**Fesoterodine**		**Trospium**		**Total**	
Oxybutynin* (N= 8,686)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients Who Switched to Each 2nd Drug	----	----	3,163	36.4%	3,066	35.3%	1,408	16.2%	345	4.0%	704	8.1%	8,686	100.0%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Dispensings of Index Drug Prior to First Switch	2	(1 - 4)	----	----	----	----	----	----	----	----	----	----	----	----
Days Between End of Index Drug Use, Dispensing Date of 2nd Drug	----	----	34	(-2 - 185)	45	(0 - 222)	45	(2 - 210)	42	(0 - 202)	35	(-2 - 148)	40	(-1 - 198)
Dispensings of 2nd Drug	----	----	2	(1 - 6)	3	(1 - 8)	3	(1 - 8)	2	(1 - 5)	2	(1 - 6)	3	(1 - 7)
Additional Dispensings of Index Drug after Switching to 2nd Drug	0	(0 - 0)	----	----	----	----	----	----	----	----	----	----	----	----

Abbreviations: IQR, Interquartile Range

* Index users with $\geq$ 2 drugs

Table D2. Pattern of Drug Dispensings, Optum Research Database: 01 January 2004 - 30 September 2012

	Second Drug Dispensed During Study Period													
Index Drug	**Oxybutynin**		**Tolterodine**		**Solifenacin**		**Darifenacin**		**Fesoterodine**		**Trospium**		**Total**	
Tolterodine* (N= 15,077)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients Who Switched to Each 2nd Drug	7,277	48.3%	----	----	4,331	28.7%	2,173	14.4%	352	2.3%	944	6.3%	15,077	100.0%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Dispensings of Index Drug Prior to First Switch	----	----	2	(1 - 6)	----	----	----	----	----	----	----	----	----	----
Days Between End of Index Drug Use, Dispensing Date of 2nd Drug	15	(-4 - 108)	----	----	43	(3 - 276)	34	(1 - 193)	140	(20 - 562)	46	(3 - 201)	28	(-1 - 177)
Dispensings of 2nd Drug	3	(1 - 9)	----	----	4	(1 - 10)	4	(1 - 9)	3	(1 - 9)	3	(1 - 7)	3	(1 - 9)
Additional Dispensings of Index Drug after Switching to 2nd Drug	----	----	0	(0 - 0)	----	----	----	----	----	----	----	----	----	----
Solifenacin* (N=6,444)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients Who Switched to Each 2nd Drug	2,800	43.5%	1,201	18.6%	----	--	1,214	18.8%	574	8.9%	655	10.2%	6,444	100.0%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Dispensings of Index Drug Prior to First Switch	----	----	----	----	2	(1 - 6)	----	----	----	----	----	----	----	----
Days Between End of Index Drug Use, Dispensing Date of 2nd Drug	17	(-6 - 102)	28	(-4 - 136)	----	----	31	(-1 - 133)	47	(5 - 194)	31	(-1 - 125)	25	(-3 - 124)
Dispensings of 2nd Drug	2	(1 - 6)	2	(1 - 6)	----	----	3	(1 - 7)	2	(1 - 6)	2	(1 - 7)	2	(1 - 6)
Additional Dispensings of Index Drug after Switching to 2nd Drug	----	----	----	----	0	(0 - 0)	----	----	----	----	----	----	----	----

Abbreviations: IQR, Interquartile Range

* Index users with $\geq$ 2 drugs

Table D2. Pattern of Drug Dispensings, Optum Research Database: 01 January 2004 - 30 September 2012

	Second Drug Dispensed During Study Period													
Index Drug	**Oxybutynin**		**Tolterodine**		**Solifenacin**		**Darifenacin**		**Fesoterodine**		**Trospium**		**Total**	
Darifenacin* (N=3,754)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients Who Switched to Each 2nd Drug	1,259	33.5%	686	18.3%	1,251	33.3%	----	----	219	5.8%	339	9.0%	3,754	100.0%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Dispensings of Index Drug Prior to First Switch	----	----	----	----	----	----	2	(1 - 6)	----	----	----	----	----	----
Days Between End of Index Drug Use, Dispensing Date of 2nd Drug	15	(-7 - 125)	27	(-3 - 131)	35	(0 - 195)	----	----	45	(2 - 240)	20	(-6 - 90)	26	(-3 - 154)
Dispensings of 2nd Drug	3	(1 - 8)	3	(1 - 7)	4	(1 - 10)	----	----	3	(1 - 7)	3	(1 - 8)	3	(1 - 8)
Additional Dispensings of Index Drug after Switching to 2nd Drug	----	----	----	----	----	----	0	(0 - 0)	----	----	----	----	----	----
Fesoterodine* (N=901)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients Who Switched to Each 2nd Drug	394	43.7%	45	5.0%	293	32.5%	115	12.8%	----	----	54	6.0%	901	100.0%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Dispensings of Index Drug Prior to First Switch	----	----	----	----	----	----	----	----	2	(1 - 3)	----	----	----	----
Days Between End of Index Drug Use, Dispensing Date of 2nd Drug	11	(-4 - 57)	-1	(-9 - 15)	16	(-1 - 49)	17	(0 - 88)	----	----	18	(-2 - 49)	12	(-3 - 57)
Dispensings of 2nd Drug	3	(1 - 6)	4	(1 - 6)	3	(1 - 7)	3	(1 - 6)	----	----	3	(1 - 4)	3	(1 - 6)
Additional Dispensings of Index Drug after Switching to 2nd Drug	----	----	----	----	----	----	----	----	0	(0 - 0)	----	----	----	----

Abbreviations: IQR, Interquartile Range

* Index users with $\geq$ 2 drugs

Table D2. Pattern of Drug Dispensings, Optum Research Database: 01 January 2004 - 30 September 2012

	Second Drug Dispensed During Study Period													
Index Drug	**Oxybutynin**		**Tolterodine**		**Solifenacin**		**Darifenacin**		**Fesoterodine**		**Trospium**		**Total**	
Trospium* (N=1,778)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients Who Switched to Each 2nd Drug	600	33.7%	280	15.7%	534	30.0%	279	15.7%	85	4.8%	----	----	1,778	100.0%
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Dispensings of Index Drug Prior to First Switch	----	----	----	----	----	----	----	----	----	----	2	(1 - 4)	----	----
Days Between End of Index Drug Use, Dispensing Date of 2nd Drug	1	(-24 - 78)	30	(-20 - 170)	26	(-14 - 167)	19	(-14 - 136)	31	(6 - 226)	----	----	15	(-18 - 136)
Dispensings of 2nd Drug	3	(1 - 8)	2	(1 - 9)	4	(1 - 9)	4	(2 - 8)	3	(1 - 6)	----	----	3	(1 - 8)
Additional Dispensings of Index Drug after Switching to 2nd Drug	----	----	----	----	----	----	----	----	----	----	0	(0 - 0)	----	----

Abbreviations: IQR, Interquartile Range

* Index users with $\geq$ 2 drugs

Table E1. Positive Predictive Values for Claims-Based Algorithms versus Adjudicated Medical Records* and Profile Review for Cardiovascular Outcomes, Within the Antimuscarinic Initiator Population, Optum Research Database: 01 January 2004 - 30 September 2012

	Claims-based Algorithm Classification				PPV (Confirmed/ Probable)†	PPV (Confirmed/ Probable + Possible)‡
	Probable	Possible	Non-cases	Total		
Acute Myocardial Infarction (Based on Algorithm B)						
Adjudicators' Case Status (Charts)						
Confirmed	13	0	0	13	100%	76.5%
Non-cases	0	4	0	4	(95% CI:100% - 100%)	(95% CI: 53.4% - 99.5%)
Total	13	4	0	17		
Principal Epidemiologists' Case Status (Claims Profiles)						
Confirmed	8	0	0	8	61.5%	47.1%
Non-cases	5	4	0	9	(95% CI: 27.8% - 95.3%)	(95% CI: 12.5% - 81.6%)
Total	13	4	0	17		
Stroke						
Adjudicators' Case Status (Charts)						
Confirmed	21	0	2	23	65.6%	65.6%
Non-cases	11	0	23	34	(95% CI: 46.6% - 84.6%)	(95% CI: 46.6% - 84.6%)
Total	32	0	25	57		
Principal Epidemiologists' Case Status (Claims Profiles)						
Confirmed	20	0	5	25	62.5%	62.5%
Non-cases	12	0	20	32	(95% CI: 43.9% - 81.1%)	(95% CI: 43.9% - 81.1%)
Total	32	0	25	57		

Abbreviations: CI, Confidence Interval; PPV, Positive Predictive Value

* The original algorithms which were used to select the charts had a PPV of 64% (AMI) and 33% (stroke). The distributions and PPVs presented in this table represent the subset of patients for which the revised algorithms were applied and for whom charts were available within the relevant time period for adjudication.

† The denominator for the PPVs in this column is the number of patients classified as Probable cases by the claims-based algorithm.

‡ The denominator for the PPVs in this column is the number of patients classified as Probable or Possible cases by the claims-based algorithm.

Table E2. Positive Predictive Values for Claims-Based Algorithms versus Adjudicated Medical Records for 10 Cancer Types and Composite Endpoint, Within the Antimuscarinic Initiator Population, Optum Research Database:
01 January 2004 - 30 September 2012

Outcome	Charts Sought (N)	Charts Obtained (N)	Non-cases (N)	Questionable (N)	Confirmed Case (N)	PPV (Confirmed/All)	95% CI	PPV (Confirmed + Questionable/All)	95% CI
Patients with No History of Cancer Reported in Baseline									
Bladder	24	17	2	0	15	88.0%	72.6% - 100%	88.0%	72.6% - 100%
Breast (Women only)	28	21	0	0	21	100%	100% - 100%	100%	100% - 100%
Colon/Rectum	18	13	1	1	11	85.0%	65.6% - 100%	92.0%	77.3% - 100%
Kidney/Renal Pelvis	25	17	1	1	15	88.0%	72.6% - 100%	94.0%	82.7% - 100%
Lung and Bronchus	23	21	4	0	17	81.0%	64.2% - 97.8%	81.0%	64.2% - 97.8%
Melanoma	26	19	1	0	18	95.0%	85.2% - 100%	95.0%	85.2% - 100%
Non-hodgkin's Lymphoma	18	15	1	1	13	87.0%	70.0% - 100%	93.0%	80.1% - 100%
Pancreatic	27	17	2	0	15	88.0%	72.6% - 100%	88.0%	72.6% - 100%
Prostate (Men only)	17	15	2	0	13	87.0%	70.0% - 100%	87.0%	70.0% - 100%
Uterine (Women only)	23	17	1	0	16	94.0%	82.7% - 100%	94.0%	82.7% - 100%
All Cancers	229	172	15	3	154	89.5%	85.0% - 94.1%	91.3%	87.1% - 95.5%

Outcome	Charts Sought (N)	Charts Obtained (N)	Non-cases (N)	Questionable (N)	Confirmed Case (N)	PPV (Confirmed/All)	95% CI	PPV (Confirmed + Questionable/All)	95% CI
Patients with a History of Cancer Reported in Baseline									
Bladder	16	15	0	0	15	100%	100% - 100%	100%	100% - 100%
Breast (Women only)	12	10	0	1	9	90.0%	71.4% - 100%	100%	100% - 100%
Colon/Rectum	22	16	1	0	15	94.0%	82.4% - 100%	94.0%	82.4% - 100%
Kidney/Renal Pelvis	15	10	3	0	7	70.0%	41.6% - 98.4%	70.0%	41.6% - 98.4%
Lung and Bronchus	17	15	3	0	12	80.0%	59.8% - 100%	80.0%	59.8% - 100%
Melanoma	14	12	0	0	12	100%	100% - 100%	100%	100% - 100%
Non-hodgkin's Lymphoma	22	18	2	3	13	72.0%	51.3% - 92.7%	89.0%	74.5% - 100%
Pancreatic	13	10	3	0	7	70.0%	41.6% - 98.4%	70.0%	41.6% - 98.4%
Prostate (Men only)	23	14	2	0	12	86.0%	67.8% - 100%	86.0%	67.8% - 100.0%
Uterine (Women only)	17	13	0	0	13	100%	100% - 100%	100%	100% - 100%
All Cancers	171	133	14	4	115	86.5%	80.7% - 92.3%	89.5%	84.3% - 94.7%

Abbreviations: PPV, Positive Predictive Value; CI, Confidence Interval

Table E2. Positive Predictive Values for Claims-Based Algorithms versus Adjudicated Medical Records for 10 Cancer Types and Composite Endpoint, Within the Antimuscarinic Initiator Population, Optum Research Database:
01 January 2004 - 30 September 2012

Outcome	Charts Sought (N)	Charts Obtained (N)	Non-cases (N)	Questionable (N)	Confirmed Case (N)	PPV (Confirmed/All)	95% CI	PPV (Confirmed + Questionable/All)	95% CI
All Patients, Regardless of Cancer History									
Bladder	40	32	2	0	30	93.8%	85.4% - 100%	93.8%	85.4% - 100%
Breast (Women only)	40	31	0	1	30	96.8%	90.6% - 100%	100%	100% - 100%
Colon/Rectum	40	29	2	1	26	89.7%	78.6% - 100%	93.1%	83.9% - 100%
Kidney/Renal Pelvis	40	27	4	1	22	81.5%	66.8% - 96.1%	85.2%	71.8% - 98.6%
Lung and Bronchus	40	36	7	0	29	80.6%	67.6% - 93.5%	80.6%	67.6% - 93.5%
Melanoma	40	31	1	0	30	96.8%	90.6% - 100%	96.8%	90.6% - 100%
Non-hodgkin's Lymphoma	40	33	3	4	26	78.8%	64.8% - 92.7%	90.9%	81.1% - 100%
Pancreatic	40	27	5	0	22	81.5%	66.8% - 96.1%	81.5%	66.8% - 96.1%
Prostate (Men only)	40	29	4	0	25	86.2%	73.7% - 98.8%	86.2%	73.7% - 98.8%
Uterine (Women only)	40	30	1	0	29	96.7%	90.2% - 100%	96.7%	90.2% - 100%
All Cancers	400	305	29	7	269	88.2%	84.6% - 91.8%	90.5%	87.2% - 93.8%

Abbreviations: PPV, Positive Predictive Value; CI, Confidence Interval

Table E3. Positive Predictive Values for Claims-Based Algorithms versus Adjudicated Medical Records for Cancer Covariates, Within the Antimuscarinic Initiator Population, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Charts Sought (N)	Charts Obtained (N)	% Obtained	Non-cases (N)	Questionable (N)	Confirmed Cases (N)	PPV (Confirmed/ All)	95% CI	PPV (Confirmed+ Questionable/All)	95% CI
Diabetes*	39	20	51.3%	0	0	20	100%	100% - 100%	100%	100% - 99.0%
Endometrial Polyps	40	31	77.5%	6	3	22	71.0%	55.0% - 86.9%	80.6%	66.7% - 94.6%
Irritable Bowel Syndrome	38	23	60.5%	11	0	12	52.2%	31.8% - 72.6%	52.2%	31.8% - 72.6%
Polycystic Ovary Disease	39	23	59.0%	5	5	13	56.5%	36.3% - 76.8%	78.3%	61.4% - 95.1%

Abbreviations: PPV, Positive Predictive Value; CI, Confidence Interval

*Three charts with insufficient information were excluded.

Table F1. Negative Predictive Values for Claims-Based Algorithms versus Adjudicated Medical Records for 10 Cancer Types and Composite Endpoint Among Patients with Evidence of Cancer During the Baseline but Who Did Not Meet the Case Definition, Optum Research Database: 01 January 2004 - 30 September 2012

Outcome	Charts Sought (N)	Charts Obtained (N)	% Obtained	Non-Cases (N)	Questionable (N)	Confirmed Cases (N)	NPV (Non-cases /Total)	95% CI	NPV (Non-cases + Questionable Cases/Total)	95% CI
Bladder	30	21	70.0%	9	0	12	42.9%	21.7% - 64.0%	42.9%	21.7% - 64.0%
Breast (Women only)	30	22	73.3%	3	1	18	13.6%	0.0% - 28.0%	18.2%	2.1% - 34.3%
Colon/Rectum	30	22	73.3%	5	1	16	22.7%	5.2% - 40.2%	27.3%	8.7% - 45.9%
Kidney/Renal Pelvis	29	19	65.5%	7	4	8	36.8%	15.2% - 58.5%	57.9%	35.7% - 80.1%
Lung and Bronchus	30	22	73.3%	13	3	6	59.1%	38.5% - 79.6%	72.7%	54.1% - 91.3%
Melanoma	30	25	83.3%	7	0	18	28.0%	10.4% - 45.6%	28.0%	10.4% - 45.6%
Non-hodgkin's Lymphoma	30	26	86.7%	15	0	11	57.7%	38.7% - 76.7%	57.7%	38.7% - 76.7%
Pancreatic	29	21	72.4%	8	5	8	38.1%	17.3% - 58.9%	61.9%	41.1% - 82.7%
Prostate (Men only)	30	27	90.0%	3	1	23	11.1%	0.0% - 23.0%	14.8%	1.4% - 28.2%
Uterine (Women only)	30	22	73.3%	3	1	18	13.6%	0.0% - 28.0%	18.2%	2.1% - 34.3%
All Cancers	298	227	76.2%	73	16	138	32.2%	26.1% - 38.2%	39.2%	32.9% - 45.6%

Abbreviations: NPV, Negative Predictive Value; CI, Confidence Interval

Table G1a. Patient Characteristics (Categorical) Reported in Chart Abstracted Data by Index Drug - Cardiovascular Charts (N = 119 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total (n, row %)	119	----	34	28.6	49	41.2	18	15.1	10	8.4	2	1.7	6	5.0
Weight Comments														
Not Recorded	75	63.0	20	58.8	32	65.3	10	55.6	7	70.0	2	100	4	66.7
Recorded	44	37.0	14	41.2	17	34.7	8	44.4	3	30.0	0	0.0	2	33.3
Underweight *	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	N/A	0	0.0
Normal Weight *	14	31.8	2	14.3	8	47.1	2	25.0	1	33.3	0	N/A	1	50.0
Overweight *	5	11.4	0	0.0	2	11.8	3	37.5	0	0.0	0	N/A	0	0.0
Obese *	24	54.5	11	78.6	7	41.2	3	37.5	2	66.7	0	N/A	1	50.0
Other *	1	2.3	1	7.1	0	0.0	0	0.0	0	0.0	0	N/A	0	0.0
Smoking Comments														
Not Recorded	17	14.3	6	17.7	9	18.4	0	0.0	0	0.0	0	0.0	2	33.3
Recorded	102	85.7	28	82.4	40	81.6	18	100.0	10	100.0	2	100.0	4	66.7
Never/non-smoker *	58	56.9	15	53.6	24	60.0	10	55.6	5	50.0	1	50.0	3	75.0
Former *	27	26.5	9	32.1	8	20.0	4	22.2	4	40.0	1	50.0	1	25.0
Current *	17	16.7	4	14.3	8	20.0	4	22.2	1	10.0	0	0.0	0	0.0
Other *	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Treatment for Alcohol														
Yes	3	2.5	1	2.9	0	0.0	2	11.1	0	0.0	0	0.0	0	0.0
No/Not recorded	116	97.5	33	97.1	49	100	16	88.9	10	100	2	100	6	100
History of:														
Diabetes														
Yes	41	34.5	11	32.4	16	32.7	9	50.0	1	10.0	1	50.0	3	50.0
No/Not Recorded	78	65.6	23	67.7	33	67.4	9	50.0	9	90.0	1	50.0	3	50.0

* Percent among those with recorded values

Table G1a. Patient Characteristics (Categorical) Reported in Chart Abstracted Data by Index Drug - Cardiovascular Charts (N = 119 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hypercholesterolemia														
Yes	58	48.7	13	38.2	22	44.9	11	61.1	7	70.0	1	50.0	4	66.7
No/Not Recorded	61	51.3	21	61.8	27	55.1	7	38.9	3	30.0	1	50.0	2	33.3
Hypertension														
Yes	88	74.0	27	79.4	36	73.5	13	72.2	6	60.0	1	50.0	5	83.3
No/Not Recorded	31	26.1	7	20.6	13	26.5	5	27.8	4	40.0	1	50.0	1	16.7
Angina														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	119	100	34	100	49	100	18	100	10	100	2	100	6	100
CABG														
Yes	23	19.3	7	20.6	11	22.5	3	16.7	1	10.0	0	0.0	1	16.7
No/Not Recorded	96	80.7	27	79.4	38	77.6	15	83.3	9	90.0	2	100	5	83.3
Arrhythmia														
Yes	24	20.2	3	8.8	12	24.5	5	27.8	2	20.0	0	0.0	2	33.3
No/Not Recorded	95	79.8	31	91.2	37	75.5	13	72.2	8	80.0	2	100	4	66.7
Congestive Heart Failure														
Yes	11	9.2	4	11.8	5	10.2	1	5.6	0	0.0	0	0.0	1	16.7
No/Not Recorded	108	90.8	30	88.2	44	89.8	17	94.4	10	100	2	100	5	83.3
Peripheral Neuropathy														
Yes	8	6.7	2	5.9	3	6.1	2	11.1	0	0.0	1	50.0	0	0.0
No/Not Recorded	111	93.3	32	94.1	46	93.9	16	88.9	10	100	1	50.0	6	100
Prostate Surgery / Cryoblation														
Yes	5	4.2	0	0.0	3	6.1	2	11.1	0	0.0	0	0.0	0	0.0
No/Not Recorded/NA	114	95.8	34	100	46	93.9	16	88.9	10	100	2	100	6	100
Neurological Disorders														
Yes	40	33.6	11	32.4	21	42.9	4	22.2	3	30.0	0	0.0	1	16.7
No/Not Recorded	79	66.4	23	67.7	28	57.1	14	77.8	7	70.0	2	100	5	83.3
Acute, Recurrent UTI														
Yes	16	13.5	5	14.7	6	12.2	3	16.7	1	10.0	0	0.0	1	16.7
No/Not Recorded	103	86.6	29	85.3	43	87.8	15	83.3	9	90.0	2	100	5	83.3

Abbreviations: CABG, Coronary Artery Bypass Graft; UTI, Urinary Tract Infection

Table G1a. Patient Characteristics (Categorical) Reported in Chart Abstracted Data by Index Drug - Cardiovascular Charts (N = 119 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Bladder Stones / Bladder Tumor														
Yes	3	2.5	2	5.9	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	116	97.5	32	94.1	48	98.0	18	100	10	100	2	100	6	100
Loop Diuretic														
Yes	22	18.5	5	14.7	11	22.5	4	22.2	1	10.0	0	0.0	1	16.7
No/Not Recorded	97	81.5	29	85.3	38	77.6	14	77.8	9	90.0	2	100	5	83.3
Digoxin														
Yes	8	6.7	2	5.9	4	8.2	2	11.1	0	0.0	0	0.0	0	0.0
No/Not Recorded	111	93.3	32	94.1	45	91.8	16	88.9	10	100	2	100	6	100
Nitrates for Cardiac Conditions														
Yes	9	7.6	3	8.8	2	4.1	1	5.6	1	10.0	0	0.0	2	33.3
No/Not Recorded	110	92.4	31	91.2	47	95.9	17	94.4	9	90.0	2	100	4	66.7
Anticoagulant														
Yes	28	23.5	5	14.7	11	22.5	6	33.3	3	30.0	0	0.0	3	50.0
No/Not Recorded	91	76.5	29	85.3	38	77.6	12	66.7	7	70.0	2	100	3	50.0
Anti-platelet Therapy (including aspirin & Plavix)														
Yes	41	34.5	10	29.4	20	40.8	6	33.3	3	30.0	0	0.0	2	33.3
No/Not Recorded	78	65.6	24	70.6	29	59.2	12	66.7	7	70.0	2	100	4	66.7
Antiarrhythmic Medications														
Yes	4	3.4	1	2.9	3	6.1	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	115	96.6	33	97.1	46	93.9	18	100	10	100	2	100	6	100
ACE Inhibitor														
Yes	26	21.9	10	29.4	8	16.3	3	16.7	2	20.0	1	50.0	2	33.3
No/Not Recorded	93	78.2	24	70.6	41	83.7	15	83.3	8	80.0	1	50.0	4	66.7
Angiotension Receptor Blocker														
Yes	25	21.0	6	17.7	11	22.5	3	16.7	3	30.0	0	0.0	2	33.3
No/Not Recorded	94	79.0	28	82.4	38	77.6	15	83.3	7	70.0	2	100	4	66.7

Abbreviations: ACE, Angiotensin-converting Enzyme

Table G1a. Patient Characteristics (Categorical) Reported in Chart Abstracted Data by Index Drug - Cardiovascular Charts (N = 119 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Beta Blocker														
Yes	40	33.6	11	32.4	16	32.7	9	50.0	3	30.0	0	0.0	1	16.7
No/Not Recorded	79	66.4	23	67.7	33	67.4	9	50.0	7	70.0	2	100	5	83.3
Calcium-channel Blocker														
Yes	31	26.1	9	26.5	13	26.5	4	22.2	2	20.0	0	0.0	3	50.0
No/Not Recorded	88	74.0	25	73.5	36	73.5	14	77.8	8	80.0	2	100	3	50.0
Thiazide Diuretic														
Yes	22	18.5	9	26.5	5	10.2	7	38.9	1	10.0	0	0.0	0	0.0
No/Not Recorded	97	81.5	25	73.5	44	89.8	11	61.1	9	90.0	2	100	6	100
Other Antihypertensive														
Yes	14	11.8	7	20.6	5	10.2	1	5.6	0	0.0	0	0.0	1	16.7
No/Not Recorded	105	88.2	27	79.4	44	89.8	17	94.4	10	100	2	100	5	83.3
Statin														
Yes	41	34.5	5	14.7	17	34.7	8	44.4	6	60.0	1	50.0	4	66.7
No/Not Recorded	78	65.6	29	85.3	32	65.3	10	55.6	4	40.0	1	50.0	2	33.3
Insulin														
Yes	16	13.5	3	8.8	8	16.3	5	27.8	0	0.0	0	0.0	0	0.0
No/Not Recorded	103	86.6	31	91.2	41	83.7	13	72.2	10	100	2	100	6	100
Oral Hypoglycemic Agent														
Yes	28	23.5	10	29.4	8	16.3	6	33.3	1	10.0	1	50.0	2	33.3
No/Not Recorded	91	76.5	24	70.6	41	83.7	12	66.7	9	90.0	1	50.0	4	66.7
Glucocorticoids														
Yes	3	2.5	0	0.0	2	4.1	1	5.6	0	0.0	0	0.0	0	0.0
No/Not Recorded	116	97.5	34	100	47	95.9	17	94.4	10	100	2	100	6	100
Low-dose Aspirin														
Yes	30	25.2	6	17.7	13	26.5	4	22.2	3	30.0	1	50.0	3	50.0
No/Not Recorded	89	74.8	28	82.4	36	73.5	14	77.8	7	70.0	1	50.0	3	50.0

Table G1b. Patient characteristics (continuous) from Chart Abstracted Data by Index Drug - Cardiovascular Charts (N = 119 Charts)

	All Abstracted Charts				
	N	**Mean**	**SD**	**Median**	**IQR**
Body Mass Index (BMI)					
All Charts with Reported Data	13 (11%)	29.2	9.3	30	(22 - 33)
Oxybutynin	3	24.3	12.1	20	(15 - 38)
Tolterodine	4	26.3	5.6	26	(22 - 31)
Solifenacin	4	30.3	6.1	31	(26 - 35)
Darifenacin	0	----	----	----	----
Fesoterodine	0	----	----	----	----
Trospium	2	40.0	14.1	40	(30 - 50)
Weight (Pounds)					
All Charts with Reported Data	79 (66%)	190.1	72.3	170	(143 - 213)
Oxybutynin	22	215.1	97.0	175	(136 - 264)
Tolterodine	28	170.8	37.2	174	(143 - 200)
Solifenacin	16	188.0	73.3	158	(146 - 207)
Darifenacin	6	174.5	82.2	149	(126 - 193)
Fesoterodine	2	207.5	3.5	208	(205 - 210)
Trospium	5	207.0	87.4	207	(145 - 246)
Height (Inches)					
All Charts with Reported Data	58 (49%)	65.8	3.7	65	(63 - 68)
Oxybutynin	16	65.6	3.8	66	(62 - 69)
Tolterodine	19	66.1	3.3	66	(63 - 68)
Solifenacin	12	63.9	3.0	63	(62 - 66)
Darifenacin	5	65.8	5.3	63	(62 - 71)
Fesoterodine	2	66.0	1.4	66	(65 - 67)
Trospium	4	70.3	4.0	69	(68 - 73)

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range

Table G2a. Patient characteristics (categorical variables) from Chart Abstracted Data by Index Drug- Cancer Charts (N= 305 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total (n, row %)	305	----	130	42.6	99	32.5	40	13.1	26	8.5	3	1.0	7	2.3
Weight Comments														
Not Recorded	195	63.9	83	63.9	66	66.7	25	62.5	14	53.9	2	66.7	5	71.4
Recorded	110	36.1	47	36.2	33	33.3	15	37.5	12	46.2	1	33.3	2	28.6
Underweight *	7	6.4	5	10.6	1	3.0	0	0.0	1	8.3	0	0.0	0	0.0
Normal Weight *	39	35.5	15	31.9	12	36.4	4	26.7	6	50.0	0	0.0	2	100
Overweight *	9	8.2	1	2.1	3	9.1	4	26.7	1	8.3	0	0.0	0	0.0
Obese *	40	36.4	19	40.4	12	36.4	5	33.3	3	25.0	1	100	0	0.0
Other *	15	13.6	7	14.9	5	15.2	2	13.3	1	8.3	0	0.0	0	0.0
Smoking Comments														
Not Recorded	92	30.2	34	26.2	29	29.3	15	37.5	9	34.6	2	66.7	3	42.9
Recorded	213	69.8	96	73.8	70	70.7	25	62.5	17	65.4	1	33.3	4	57.1
Never/non-smoker *	104	48.8	42	43.8	34	48.6	14	56.0	11	64.7	0	0.0	3	75.0
Former *	74	34.7	36	37.5	23	32.9	10	40.0	3	17.6	1	100	1	25.0
Current *	34	16.0	18	18.8	12	17.1	1	4.0	3	17.6	0	0.0	0	0.0
Other *	1	0.5	0	0.0	1	1.4	0	0.0	0	0.0	0	0.0	0	0.0
History of:														
Treatment for Alcohol														
Yes	12	3.9	6	4.6	5	5.1	1	2.5	0	0.0	0	0.0	0	0.0
No/Not Recorded	293	96.1	124	95.4	94	95.0	39	97.5	26	100	3	100	7	100
Hormone Replacement Therapy														
Yes	24	7.9	8	6.2	8	8.1	2	5.0	4	15.4	1	33.3	1	14.3
No/Not Recorded	281	92.1	122	93.9	91	91.9	38	95.0	22	84.6	2	66.7	6	85.7
Family History of Cancer														
Yes	95	31.2	44	33.9	29	29.3	9	22.5	10	38.5	1	33.3	2	28.6
No/Not Recorded	210	68.9	86	66.2	70	70.7	31	77.5	16	61.5	2	66.7	5	71.4

* Percent among those with recorded values

Table G2a. Patient characteristics (categorical variables) from Chart Abstracted Data by Index Drug- Cancer Charts (N= 305 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Occupational Exposure to Radiation														
Yes	1	0.3	1	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	304	99.7	129	99.2	99	100	40	100	26	100	3	100	7	100
Chronic Liver Disease														
Yes	11	3.6	4	3.1	4	4.0	1	2.5	1	3.9	1	33.3	0	0.0
No/Not Recorded	294	96.4	126	96.9	95	96.0	39	97.5	25	96.2	2	66.7	7	100
Viral Hepatitis														
Yes	5	1.6	1	0.8	4	4.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	300	98.4	129	99.2	95	96.0	40	100	26	100	3	100	7	100
Dementia														
Yes	2	0.7	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	303	99.3	128	98.5	99	100	40	100	26	100	3	100	7	100
Gout														
Yes	7	2.3	2	1.5	4	4.0	1	2.5	0	0.0	0	0.0	0	0.0
No/Not Recorded	298	97.7	128	98.5	95	96.0	39	97.5	26	100	3	100	7	100
Inflammatory Arthritis or Use of Associated Medications														
Yes	1	0.3	0	0.0	0	0.0	1	2.5	0	0.0	0	0.0	0	0.0
No/Not Recorded	304	99.7	130	100	99	100	39	97.5	26	100	3	100	7	100
Dialysis														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	305	100	130	100	99	100	40	100	26	100	3	100	7	100
Chronic Obstructive Pulmonary Disease														
Yes	20	6.6	8	6.2	6	6.1	4	10.0	2	7.7	0	0.0	0	0.0
No/Not Recorded	285	93.4	122	93.9	93	93.9	36	90.0	24	92.3	3	100	7	100
Asthma														
Yes	14	4.6	5	3.9	8	8.1	0	0.0	0	0.0	0	0.0	1	14.3
No/Not Recorded	291	95.4	125	96.2	91	91.9	40	100	26	100	3	100	6	85.7

Table G2a. Patient characteristics (categorical variables) from Chart Abstracted Data by Index Drug- Cancer Charts (N= 305 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thyroid Replacement or Hypothyroidism														
Yes	29	9.5	11	8.5	8	8.1	4	10.0	4	15.4	0	0.0	2	28.6
No/Not Recorded	276	90.5	119	91.5	91	91.9	36	90.0	22	84.6	3	100	5	71.4
Frequent UTI														
Yes	10	3.3	4	3.1	5	5.1	0	0.0	1	3.9	0	0.0	0	0.0
No/Not Recorded	295	96.7	126	96.9	94	95.0	40	100.0	25	96.2	3	100	7	100
Menopause														
Yes	40	13.1	15	11.5	13	13.1	6	15.0	3	11.5	1	33.3	2	28.6
No/Not Recorded	265	86.9	115	88.5	86	86.9	34	85.0	23	88.5	2	66.7	5	71.4
Diabetes														
Yes	47	15.4	21	16.2	14	14.1	6	15.0	4	15.4	1	33.3	1	14.3
No/Not Recorded	258	84.6	109	83.9	85	85.9	34	85.0	22	84.6	2	66.7	6	85.7
Inflammatory Bowel Disease														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	305	100	130	100	99	100	40	100	26	100	3	100	7	100
Autoimmune Conditions														
Yes	10	3.3	6	4.6	2	2.0	2	5.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	295	96.7	124	95.4	97	98.0	38	95.0	26	100	3	100	7	100
Bone Marrow or Organ Transplant														
Yes	2	0.7	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	303	99.3	128	98.5	99	100	40	100	26	100	3	100	7	100
Immunosuppressive Therapy														
Yes	1	0.3	1	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	304	99.7	129	99.2	99	100	40	100	26	100	3	100	7	100
H. Pylori Infection														
Yes	2	0.7	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	303	99.3	128	98.5	99	100	40	100	26	100	3	100	7	100

Abbreviations: UTI, Urinary Tract Infection

Table G2a. Patient characteristics (categorical variables) from Chart Abstracted Data by Index Drug- Cancer Charts (N= 305 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anabolic Steroid Usage														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	305	100	130	100	99	100	40	100	26	100	3	100	7	100
Colorectal Polyps														
Yes	18	5.9	3	2.3	9	9.1	5	12.5	0	0.0	1	33.3	0	0.0
No/Not Recorded	287	94.1	127	97.7	90	90.9	35	87.5	26	100	2	66.7	7	100
Bladder Stones / Polyps														
Yes	3	1.0	2	1.5	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	302	99.0	128	98.5	98	99.0	40	100	26	100	3	100	7	100
Excision of Skin Cancers (Melanoma, Basal cell, Squamous Cell)														
Yes	32	10.5	15	11.5	12	12.1	2	5.0	2	7.7	0	0.0	1	14.3
No/Not Recorded	273	89.5	115	88.5	87	87.9	38	95.0	24	92.3	3	100	6	85.7
Benign Prostatic Hyperplasia (BPH)														
Yes	5	1.6	1	0.8	3	3.0	0	0.0	1	3.9	0	0.0	0	0.0
No/Not Recorded	300	98.4	129	99.2	96	97.0	40	100	25	96.2	3	100	7	100
Prostatitis														
Yes	2	0.7	0	0.0	1	1.0	1	2.5	0	0.0	0	0.0	0	0.0
No/Not Recorded	303	99.3	130	100	98	99.0	39	97.5	26	100	3	100	7	100
BRCA1 Mutation (Report of positive test)														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	305	100	130	100	99	100	40	100	26	100	3	100	7	100
BRCA2 Mutation (Report of positive test)														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	305	100	130	100	99	100	40	100	26	100	3	100	7	100

Table G2a. Patient characteristics (categorical variables) from Chart Abstracted Data by Index Drug- Cancer Charts (N= 305 Charts)

	All Abstracted charts													
	All		Oxybutynin		Tolterodine		Solifenacin		Darifenacin		Fesoterodine		Trospium	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Polycystic Ovary Syndrome														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	305	100	130	100	99	100	40	100	26	100	3	100	7	100
Tamoxifen, Aromatase Inhibitor, or Estrogen Receptor Antagonist														
Yes	10	3.3	3	2.3	1	1.0	2	5.0	2	7.7	1	33.3	1	14.3
No/Not Recorded	295	96.7	127	97.7	98	99.0	38	95.0	24	92.3	2	66.7	6	85.7
Fertility Treatments														
Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No/Not Recorded	305	100	130	100	99	100	40	100	26	100	3	100	7	100

Table G2b. Patient Characteristics (continuous) from Chart Abstracted Data by Index Drug - Cancer Charts (N= 305 Charts)

	All Abstracted Charts				
	N	Mean	SD	Median	IQR
Body Mass Index (BMI)					
All Charts with Reported Data	36 (12%)	31.0	7.5	31	(26 - 36)
Oxybutynin	17	32.0	7.0	31	(27 - 38)
Tolterodine	11	31.9	9.0	32	(25 - 36)
Solifenacin	5	29.2	6.7	28	(26 - 30)
Darifenacin	2	22.0	4.2	22	(19 - 25)
Fesoterodine	0	----	----	----	----
Trospium	1	31.0	----	31	(31 - 31)
Weight (Pounds)					
All Charts with Reported Data	191 (63%)	189.3	52.3	178	(156 - 219)
Oxybutynin	77	187.3	50.3	180	(160 - 215)
Tolterodine	65	193.2	55.9	178	(145 - 224)
Solifenacin	28	184.9	46.8	177	(157 - 212)
Darifenacin	14	185.6	62.3	166	(155 - 189)
Fesoterodine	3	199.6	67.7	204	(130 - 265)
Trospium	4	201.6	42.3	196	(174 - 230)
Height (Inches)					
All Charts with Reported Data	139 (46%)	66.7	4.0	66	(63 - 69)
Oxybutynin	55	67.1	3.8	67	(64 - 69)
Tolterodine	51	66.5	4.1	66	(63 - 69)
Solifenacin	18	65.2	4.1	65	(62 - 67)
Darifenacin	10	68.2	4.2	68	(65 - 71)
Fesoterodine	1	72.0	----	72	(72 - 72)
Trospium	4	64.5	3.1	65	(62 - 67)

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range

Table G3a. Baseline* Characteristics (Categorical) Among Patients Eligible for Cancer Chart Abstraction, Optum Research Database: 01 January 2004 - 30 September 2012

	Any of Top 10 Cancers During Follow-up		Charts Sought		Charts Obtained	
	N = 4,614		N = 400		N = 305	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Overall						
Age						
18-44	180	3.9	18	4.5	12	3.9
45-54	720	15.6	78	19.5	64	21.0
55-64	1,790	38.8	189	47.3	136	44.6
65-74	971	21.0	80	20.0	65	21.3
75+	953	20.7	35	8.8	28	9.2
Gender						
Female	2,205	47.8	214	53.5	160	52.5
Male	2,409	52.2	186	46.5	145	47.5
Alcohol Use / Abuse						
Yes	28	0.6	4	1.0	4	1.3
No	4,586	99.4	396	99.0	301	98.7
Smoking						
Yes	195	4.2	20	5.0	18	5.9
No	4,419	95.8	380	95.0	287	94.1
Overweight / Obesity						
Yes	166	3.6	13	3.3	13	4.3
No	4,448	96.4	387	96.8	292	95.7
Chronic Obstructive Pulmonary Disease						
Yes	229	5.0	22	5.5	17	5.6
No	4,385	95.0	378	94.5	288	94.4
Renal Impairment / Dialysis						
Yes	217	4.7	30	7.5	18	5.9
No	4,397	95.3	370	92.5	287	94.1
Diabetes						
Yes	598	13.0	60	15.0	46	15.1
No	4,016	87.0	340	85.0	259	84.9

* Baseline period began July 1, 2003.

Table G3a. Baseline* Characteristics (Categorical) Among Patients Eligible for Cancer Chart Abstraction, Optum Research Database: 01 January 2004 - 30 September 2012

	Any of Top 10 Cancers During Follow-up		Charts Sought		Charts Obtained	
	N = 4,614		N = 400		N = 305	
Baseline Patient Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Endometrial Polyps (Women only)						
Yes	4	0.2	0	0.0	0	0.0
No	2,201	99.8	214	100.0	160	100.0
Irritable Bowel Syndrome						
Yes	53	1.2	1	0.3	1	0.3
No	4,561	98.9	399	99.8	304	99.7
Polycystic Ovary Syndrome (Women only)						
Yes	0	0.0	0	0.0	0	0.0
No	2,205	100.0	214	100.0	160	100.0
Any Cancer Drug						
Yes	377	8.2	45	11.3	35	11.5
No	4,237	91.8	355	88.8	270	88.5
Alkylating Agents						
Yes	6	0.1	4	1.0	4	1.3
No	4,608	99.9	396	99.0	301	98.7
Antimetabolites						
Yes	70	1.5	10	2.5	6	2.0
No	4,544	98.5	390	97.5	299	98.0
Antimicrotubule Agents						
Yes	0	0.0	0	0.0	0	0.0
No	4,614	100.0	400	100.0	305	100.0
Topoisomerase-active Agents						
Yes	0	0.0	1	0.3	1	0.3
No	4,614	100.0	399	99.8	304	99.7
Antineoplastic Antibiotics						
Yes	0	0.0	0	0.0	0	0.0
No	4,614	100.0	400	100.0	305	100.0
Endocrine Agents						
Yes	303	6.6	28	7.0	23	7.5
No	4,311	93.4	372	93.0	282	92.5
Biologically-directed Therapies						
Yes	4	0.1	7	1.8	6	2.0
No	4,610	99.9	393	98.3	299	98.0
Immune Therapies						
Yes	5	0.1	1	0.3	0	0.0
No	4,609	99.9	399	99.8	305	100.0
Miscellaneous Agents						
Yes	0	0.0	0	0.0	0	0.0
No	4,614	100.0	400	100.0	305	100.0

* Baseline period began July 1, 2003.

Table G3b. Baseline* Characteristics (Continuous) Among Patients Eligible for Cancer Chart Abstraction, Optum Research Database: 01 January 2004 - 30 September 2012

Baseline Patient Characteristics	Any of Top 10 Cancers During Follow-up N = 4,614		Charts Sought N = 400		Charts Obtained N = 305	
	Median	IQR	Median	IQR	Median	IQR
Membership† Length (Months)	34	(17 - 57)	28	(15 - 52)	30	(16 - 52)
Number of Days in Hospital During Baseline (Entire Cohort)	0	(0 - 0)	0	(0 - 2)	0	(0 - 3)
Number of Days in Hospital During Baseline (Among Patients with at least 1 Day)	3	(2 - 6)	4	(2 - 9)	4	(2 - 9)
Total Health Care Costs ($)	4,208	(1,821 - 10,370)	9,768	(3,793 - 29,995)	10,716	(4,141 - 32,821)
Total Drug Costs ($)	980	(400 - 1,953)	1,087	(422 - 2,306)	1,164	(430 - 2,348)
Number of Unique ICD-9 Diagnosis Codes in Baseline (3-Digit Level)	49	(33 - 69)	52	(35 - 68)	52	(35 - 67)
Number of Unique Drugs Dispensed in Baseline (HICL Level)	8	(5 - 11)	9	(6 - 13)	9	(6 - 13)
Number of Unique Laboratory Tests in Baseline	18	(10 - 32)	25	(15 - 42)	25	(15 - 43)

Abbreviations: HICL, Hierarchical Ingredient Code List; IQR, Interquartile Range

* Baseline period began July 1, 2003.

† Membership from start of enrollment through index date

Table H1. Overlap* of Claims-Identified Multiple Outcomes and Distribution of Associated Person-Time. Optum Research Database: 01 January 2004 - 30 September 2012

					Person-time Between Outcomes (Days)			
	N During Study Period		N During Study Period	Patients with Multiple Outcomes During Follow-up (N)	Median	IQR	Mean	Range
First Event		**Second Event**						
Any Cancer[†]	4,612	Any MACE Event	3,067	100	260	(68 - 766)	515.3	(0 - 2,384)
Any Cancer	4,612	AMI	1,535	61	362	(76 - 933)	572.8	(0 - 2,384)
Any Cancer	4,612	Stroke	1,474	33	194	(58 - 481)	363.4	(0 - 2,287)
Any Cancer	4,612	CV Death	308	6	858	(192 - 1,015)	766.0	(24 - 1,650)
Any Cancer	4,612	All Cause Mortality	1,769	116	197	(89 - 479)	370.5	(0 - 1,856)
Any MACE Event	3,067	Any Cancer	4,612	49	126	(40 - 432)	323.6	(18 - 1,444)
AMI	1,535	Any Cancer	4,612	24	123	(58 - 597)	394.1	(23 - 1,444)
Stroke	1,474	Any Cancer	4,612	23	152	(40 - 426)	275.0	(18 - 1,012)
Any MACE Event	3,067	All Cause Mortality	1,769	398	0	(0 - 18)	108.4	(0 - 2,397)
AMI	1,535	Stroke	1,474	51	9	(1 - 242)	195.1	(0 - 2,035)
AMI	1,535	CV Death	308	101	1	(0 - 19)	79.8	(0 - 1,296)
AMI	1,535	All Cause Mortality	1,769	61	57	(5 - 323)	296.6	(0 - 2,397)
Stroke	1,474	AMI	1,535	31	204	(14 - 443)	322.6	(1 - 2,035)
Stroke	1,474	CV Death	308	52	0	(0 - 1)	37.1	(0 - 1,725)
Stroke	1,474	All Cause Mortality	1,769	36	51	(10 - 265)	249.3	(0 - 2,082)

Abbreviations: AMI, Acute Myocardial Infarction; CV, Cardiovascular Disease; IQR, Interquartile Range; MACE, Major Adverse Cardiac Events

* The overlap is limited to the first two outcomes.

[†] Includes only patients who do not meet the definition for baseline cancer or who do not have V10 (history of cancer) in baseline period.

Table H2: Chart Procurement Rates by Site of Service and Outcome. Optum Research Database, 01 January 2004 - 30 September 2012

	Outcome							
	Cancer		Cardiovascular		Non-cancer		Covariates	
Site of Service	N*	%	N*	%	N*	%	N*	%
Original Site of Chart Request								
Inpatient								
Sought	181	----	137	----	81	----	31	----
Obtained	128	41.4	93	40.4	61	43.0	21	40.4
Outpatient								
Sought	219	----	21	----	217	----	125	----
Obtained	134	38.0	10	32.3	131	37.6	56	30.9
Alternate Site of Chart Request								
Inpatient								
Sought	7	----	5	----	5	----	9	----
Obtained	2	22.2	3	37.5	1	16.7	3	25.0
Outpatient								
Sought	99	----	43	----	73	----	54	----
Obtained	41	29.3	13	23.2	34	31.8	20	27.0
Total Patients for Whom Charts were Sought	400		158		298		156	
Total Unique Patient Charts Obtained	305		119		227		100	
% of Patients for Whom Charts were Obtained	76%		75%		76%		64%	
% of Charts With Original Request from Inpatient Site	45%		87%		27%		20%	

* Number of charts

11. Appendix 1 – CV Algorithms

Excerpt from Full-Study Statistical Analysis Plan V1.5

4.6.1 Cardiovascular

For this validation study, the components of Major Adverse Cardiac Events (MACE), a composite MACE outcome, and all-cause mortality will be examined separately, as defined below:

- Acute myocardial infarction (AMI)
- Stroke
- CV mortality
  - Coronary heart disease death
  - Cerebrovascular death
- A composite outcome "Any MACE event (AMI, Stroke, or CV mortality)"
- All-cause mortality

During the initial proposal and protocol development period, it was determined that death would be assessed on the claims-level only (as defined in Section 4.6.1.3) during the validation study. In contrast, the design and timeline for Protocols 178-CL-113 and 178-CL-114 includes validation of death through a National Death Index (NDI) search.

4.6.1.1 AMI Algorithm

In initial versions of the protocol, AMI was defined by having at least one claim with an ICD-9 code 410.xx in the first or second position of the hospital or Emergency Room diagnosis. Preliminary analyses suggested that additional refinements to the AMI algorithm would be necessary due to lower than anticipated PPVs.

Two additional proposed algorithms are presented in this SAP. The first AMI algorithm (referred to as algorithm A) will be defined based on diagnostic codes only (ICD-9 and Diagnostic Related Groups (DRG) codes.) Because some AMIs are averted by the intervention of revascularization procedures, a second algorithm (algorithm B), which includes revascularization procedure-related codes, also will be considered to capture these events. Both algorithms will consider the occurrence of death.

AMI Algorithm A:

Probable cases will include patients with:

(1) 2+ claims with AMI ICD-9 codes

or

(2) 1 claim with an AMI code along with claims for death[a]

or

(3) a DRG consistent with AMI.

[a] The algorithm for identifying deaths is described in section 4.6.1.3. Only deaths within 30 days of claims with an AMI code will be included in deaths for the AMI algorithm.

Possible cases will include patients with:

(1) one claim with an AMI ICD-9 code
and
(2) no claims for death
and
(3) no DRG consistent with AMI

Non-cases will include patients without claims with AMI ICD-9 or DRG codes.

AMI Algorithm B:

Probable cases will include patients with:

(1) 2+ claims with AMI codes,
or
(2) 1 claim with an AMI code along with claims for death or revascularization),
or
(3) a DRG consistent with AMI or revascularization

Possible cases will include patients with:

(1) one claim with an AMI code and no claims for death or revascularization
and
(2) no DRGs consistent with AMI or revascularization

Non-cases will include patients with no claims with AMI codes and no claims with a DRG consistent with AMI or revascularization

Codes included in the CV algorithms

ICD-9 diagnosis codes for AMI are restricted to:

410.x0	Acute myocardial infarction, episode of care unspecified
410.x1	Acute myocardial infarction, initial episode of care

Only claims from an ER or inpatient setting, with AMI diagnosis codes listed in the first or second position will be included.

The DRGs to be considered for AMI include:

Year	Code	Description
2003-2007*		
	121	CIRCULATORY DISORDERS W AMI & MAJOR COMP, DISCHARGED ALIVE
	122	CIRCULATORY DISORDERS W AMI W/O MAJOR COMP, DISCHARGED ALIVE

	123	CIRCULATORY DISORDERS W AMI, EXPIRED
2007*-2012		
	280	AMI, DISCHARGED ALIVE W MAJOR COMPLICATIONS
	281	AMI, DISCHARGED ALIVE W COMPLICATIONS
	282	AMI, DISCHARGED ALIVE WO COMPLICATIONS
	283	AMI, EXPIRED W MAJOR COMPLICATIONS
	284	AMI, EXPIRED W COMPLICATIONS
	285	AMI, EXPIRED WO COMPLICATIONS

*Codes differ within 2007 due to fiscal year timing. Corresponding adjustments will be made based on event date.

The CPT, ICD-9 procedure and HCPCS codes for revascularization are provided in Appendix 4 of the SAP, Revascularization Codes (and Appendix 2 of the Study Report).

The DRG codes for revascularization include:

Year	**Code**	**Description**
2004-2007*		
	110	MAJOR CARDIOVASCULAR PROCEDURES WITH COMPLICATIONS
	111	MAJOR CARDIOVASCULAR PROCEDURES W/O COMPLICATIONS
	233	CORONARY BYPASS W CARDIAC CATHETERIZATION W MAJOR COMPLICATIONS
	555	PERCUTANEOUS CARDIOVASCULAR PROCEDURE W MAJOR CV DIAGNOSIS
	556	PERCUTANEOUS CARDIOVASC PROCEDURE W NON-DRUG-ELUTING STENT W/O MAJ CV DIAGNOSIS
	557	PERCUTANEOUS CARDIOVASCULAR PROCEDURE W DRUG-ELUTING STENT W MAJOR CV DIAGNOSIS
	558	PERCUTANEOUS CARDIOVASCULAR PROCEDURE W DRUG-ELUTING STENT W/O MAJ CV DIAGNOSIS

2007*-2012

222	CARD DEFIB W CATH W AMI/HF/SHOCK W MAJOR COMPLICATIONS
231	CORONARY BYPASS W PTCA W MAJOR COMPLICATIONS
233	CORONARY BYPASS W CARD CATH W MAJOR COMPLICATIONS
237	MAJOR CARDIOVASC PROC W MAJOR COMPLICATIONS OR THOR AA REP
238	MAJOR CARDIOVASCULAR PROCEDURE WO MAJOR COMPLICATIONS
555	PERC CV PROCEDURE W MAJOR CV DIAGNOSES

*Codes differ within 2007 due to fiscal year timing. Corresponding adjustments will be made based on event date.

4.6.1.2 Stroke Algorithm

In initial versions of the protocol, stroke was defined by having at least one claim with a diagnosis codes of 430, 431, 433.x1, 434.x1 or 436, located in the first position only of the hospital or Emergency Room diagnosis. Preliminary analyses suggested that additional refinements to the stroke algorithm would be necessary, due to changes in ICD-9 coding and low PPVs. A revised algorithm is presented below.

Patients with any of the following baseline characteristics will be excluded prior to the implementation of the stroke algorithm:

- history of stroke, defined as the presence of a claims with a diagnosis code for ischemic or hemorrhagic stroke
- the presence of at least one code indicating a prior cancer diagnosis, (ICD-9: 140-239, or V10 (history of malignancy))
- at least one dispensing for warfarin
- a code for atrial fibrillation (ICD-9: 427.31)

The algorithm will consider diagnosis, procedure and DRG codes related to ischemic and hemorrhagic strokes. Also considered will be claims for medical imaging and medical, physical and occupational therapies or equipment after the potential stroke is identified.

The algorithm for stroke will be defined in the following way:

Probable cases will be defined by the presence of claims with:

(1) at least one ischemic ICD-9 code or at least one hemorrhagic ICD-9 code (without head injury)

and

(2) at least one claim with a code indicative of medical imaging, post-stroke physical or occupational therapy or equipment, anticoagulant medical therapy(for ischemic strokes only) or death[b]

or

(3) at least one claim with a DRG for stroke

Possible cases will be defined by:

(1) the *presence* of at least one claim with an ischemic code or at least one hemorrhagic code (without head injury)

and

(2) the *absence* of claims with codes indicative of scans, post-stroke physical or occupational therapy or equipment, anticoagulant medical therapy (for ischemic strokes only), or death

[b] The algorithm for identifying deaths is described in section 4.6.1.3. Only deaths within 30 days of claims with a hemorrhagic or ischemic code will be included in deaths for the stroke algorithms.

Non-cases will be defined by:

(1) the *absence* of any claims with ischemic or hemorrhagic codes
and
(2) the *absence* of claims with a DRG for stroke
or
(3) the *presence* of a hemorrhagic code and a qualifying head injury code

Codes included in the stroke algorithm

Ischemic ICD-9 diagnosis codes (restricted to inpatient or ER claims, primary position)

433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral pre-cerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified pre-cerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified pre-cerebral artery with cerebral infarction
434.01	Cerebral thrombosis with cerebral infarction
434.11	Cerebral embolism with cerebral infarction
434.91	Cerebral artery occlusion, unspecified with cerebral infarction

Hemorrhagic ICD-9 diagnosis codes (restricted to inpatient or ER claims, primary position)

430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432.1	Subdural hemorrhage
432.9	Unspecified intracranial hemorrhage

Patients with at least one claim with a hemorrhagic code, but also having a claim with diagnosis of traumatic head injury within 60 days prior to (and including) the date of diagnosis of potential stroke will be determined to be non-cases. There will be no site-of care or position restrictions for the head injury claims.

Head Injury ICD-9 diagnosis codes

800-804	Fracture of skull
850-854	Intracranial Injury, excluding those with skull fracture

Medical imaging will be defined as the presence of at least one claim for CT scan of the head or MRI scan of the brain within 60 days before or after (and including) the date of diagnosis of stroke (based on earliest ischemic or hemorrhagic claim.) There will be no site-of-care or position restrictions for the imagine procedures

Medical Imaging CPT /ICD-9 procedure codes

70450	CT scan of head without contrast
70460	CT scan of head with contrast

70470	CT scan of head with and without contrast
70551	MRI of brain without contrast
70552	MRI of brain with contrast only
70553	MRI of brain with and without contrast
93880	Duplex scan extracranial arteries, complete bilateral series
87.03	CT of head
88.91	MRI imaging of brain and brain stem
88.41	Arteriogram of cerebral artery
88.71	Diagnostic ultrasound of head

Medical therapies will be defined by claims evidence for any one or more of the following anticoagulation therapies within 60 days after (and including) the date of diagnosis of stroke (based on earliest ischemic claim.) There will be no site-of-care or position restrictions for the therapy claims.

Anticoagulant Medical Therapy Codes

J1644, J1642	Heparin (injection, HCPCS codes:)
99.10	Injection of thrombolytic agent (ICD-9 procedure code)
V58.66	Long-term use of aspirin (ICD-9 diagnosis code)
	Alteplase (based on HICLs)
	Anticoagulants (based on HICLs)
	Heparin (based on HICLs)
	Warfarin (based on HICLs)

Physical or occupational therapies or equipment will be defined by claims evidence for any one or more of the following therapies within 60 days after (and including) the date of diagnosis of stroke (based on earliest ischemic or hemorrhagic claim.) There will be no site-of-care or position restrictions for these claims.

Physical or Occupational Therapy or Equipment Codes

97110-97546	Therapeutic procedures (ICD-9 procedure code)
S9131	PT, at home (HCPCS code)
S9129	Occupational therapy (at home) (HCPCS code)
S9128	Speech therapy (at home) (HCPCS code)
93.75	Other speech training and therapy (ICD-9 procedure code)
438	Late effects of cerebrovascular disease, including cognitive, speech, hemiplegia, monoplegia and other paralytic syndromes. (ICD-9 diagnosis code)
V57x	Rehab services (ICD-9 diagnosis code)
K000x	Wheelchair (HCPCS code)
E0143, A4637, E0135	Walker (HCPCS code)

For stroke, the DRGs to be considered include:

Year	Code	Description
2004-2007*		
	014	INTRACRANIAL HEMORRHAGE OR CEREBRAL INFARCTION
	559	ACUTE ISCHEMIC STROKE WITH USE OF THROMBOLYTIC AGENT
2007*-2012		
	061	ACUTE ISCHEMIC STROKE W USE OF THROMBOLYTIC AGENT W MAJOR COMPLICATIONS
	062	ACUTE ISCHEMIC STROKE W USE OF THROMBOLYTIC AGENT W COMPLICATIONS
	063	ACUTE ISCHEMIC STROKE W USE OF THROMBOLYTIC AGENT W/O COMPLICATIONS
	064	INTRACRANIAL HEMORRHAGE OR CEREBRAL INFARCTION W MAJOR COMPLICATIONS
	065	INTRACRANIAL HEMORRHAGE OR CEREBRAL INFARCTION
	066	INTRACRANIAL HEMORRHAGE OR CEREBRAL INFARCTION WO COMPLICATIONS

*Codes differ within 2007 due to fiscal year timing. Corresponding adjustments will be made based on date of event.

4.6.1.3 All-cause Mortality

Patient death will be defined by:

(1) One or more inpatient or ER claim with patient status listed with the following discharge status UB92 codes:

20 = expired

40 = expired at home

41 = expired in medical facility

42 = expired – place unknown

or

(2) At least one claim with ICD-9 diagnosis code 798.XX (sudden death) or 427.5 (cardiac arrest)

and

(3) No claims on dates more than 30 days after (1) or (2)[c]

[c] Note: There is a 30 day grace period for claims to accrue after the date of patient status=expired or ICD-9=798,427.5

4.6.1.4 CV Mortality

CV mortality will be defined based on the presence of an indicator for death (as defined in Section 4.6.1.3) and at least one of the following codes within 7 days prior or 30 days after the date of death. Two types of death will be combined into the CV mortality definition.

Coronary heart disease death

ICD-9 diagnosis codes

411.xx	Other acute and subacute forms of ischemic heart disease
413.xx	Angina pectoris
414.xx	Other forms of chronic ischemic heart disease

Cerebrovascular death

ICD-9 diagnosis codes

430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432.1	Subdural hemorrhage
432.9	Unspecified intracranial hemorrhage
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral pre-cerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified pre-cerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified pre-cerebral artery with cerebral infarction
434.01	Cerebral thrombosis with cerebral infarction
434.11	Cerebral embolism with cerebral infarction
434.91	Cerebral artery occlusion, unspecified with cerebral infarction

However, deaths associated with accidents (defined by the presence of a claim with an ICD-9 code beginning with E (external causes of injury) in the 7 days prior or 30 days after the date of death), or malignancy (defined by the presence of a claim with a malignancy code (140 – 239.9) in the 7 days prior or 30 days after the date of death), will NOT be counted as cardiovascular deaths.

4.6.1.5 MACE Composite Endpoint[d]

The composite outcome major adverse cardiac events (MACE)—acute myocardial infarction, stroke, or CV mortality—will be examined. A binary indicator of "any MACE event, yes/no" will be created. Person-time will stop accruing on the date of the first MACE event.

[d] This composite measure has been added, per Astellas' request, and was not included in earlier versions of the protocol or SAP

12. Appendix 2 – Revascularization Codes

Description	Code Type	Code
Endoscopic transmyocardial revascularization	ICD-9 Proc	36.33
Transmyocardial laser revascularization, by thoracotomy; performed at the time of other open cardiac procedure(s) (List separately in addition to code for primary procedure)	CPT	33141
Endoscopy, surgical, including video-assisted harvest of vein(s) for coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT	33508
Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft (List separately in addition to code for primary procedure)	CPT	33517
Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts (List separately in addition to code for primary procedure)	CPT	33518
Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts (List separately in addition to code for primary procedure)	CPT	33519
Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts (List separately in addition to code for primary procedure)	CPT	33521
Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts (List separately in addition to code for primary procedure)	CPT	33522
Coronary artery bypass, using venous graft(s) and arterial graft(s); 6 or more venous grafts (List separately in addition to code for primary procedure)	CPT	33523
Reoperation, coronary artery bypass procedure or valve procedure, more than 1 month after original operation (List separately in addition to code for primary procedure)	CPT	33530
Coronary endarterectomy, open, any method, of left anterior descending, circumflex, or right coronary artery performed in conjunction with coronary artery bypass graft procedure, each vessel (List separately in addition to primary procedure)	CPT	33572
Harvest of upper extremity vein, 1 segment, for lower extremity or coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT	35500
Harvest of femoropopliteal vein, 1 segment, for vascular reconstruction procedure (eg, aortic, vena caval, coronary, peripheral artery) (List separately in addition to code for primary procedure)	CPT	35572
Harvest of upper extremity artery, 1 segment, for coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT	35600
Open chest coronary artery angioplasty	ICD-9 Proc	36.03
Other removal of coronary artery obstruction	ICD-9 Proc	36.09
Aortocoronary bypass for heart revascularization, not otherwise specified	ICD-9 Proc	36.1
(Aorto)coronary bypass of one coronary artery	ICD-9 Proc	36.11
(Aorto)coronary bypass of two coronary arteries	ICD-9 Proc	36.12
(Aorto)coronary bypass of three coronary arteries	ICD-9 Proc	36.13
(Aorto)coronary bypass of four or more coronary arteries	ICD-9 Proc	36.14
Single internal mammary-coronary artery bypass	ICD-9 Proc	36.15
Double internal mammary-coronary artery bypass	ICD-9 Proc	36.16
Abdominal-coronary artery bypass	ICD-9 Proc	36.17
Other bypass anastomosis for heart revascularization	ICD-9 Proc	36.19

Description	Code Type	Code
Heart revascularization by arterial implant	ICD-9 Proc	36.2
Open chest transmyocardial revascularization	ICD-9 Proc	36.31
Anesthesia for direct coronary artery bypass grafting; without pump oxygenator	CPT	566
Anesthesia for direct coronary artery bypass grafting; with pump oxygenator	CPT	567
Transmyocardial laser revascularization, by thoracotomy; (separate procedure)	CPT	33140
Coronary artery bypass, vein only; single coronary venous graft	CPT	33510
Coronary artery bypass, vein only; 2 coronary venous grafts	CPT	33511
Coronary artery bypass, vein only; 3 coronary venous grafts	CPT	33512
Coronary artery bypass, vein only; 4 coronary venous grafts	CPT	33513
Coronary artery bypass, vein only; 5 coronary venous grafts	CPT	33514
Coronary artery bypass, vein only; 6 or more coronary venous grafts	CPT	33516
Coronary artery bypass, using arterial graft(s); single arterial graft	CPT	33533
Coronary artery bypass, using arterial graft(s); 2 coronary arterial grafts	CPT	33534
Coronary artery bypass, using arterial graft(s); 3 coronary arterial grafts	CPT	33535
Coronary artery bypass, using arterial graft(s); 4 or more coronary arterial grafts	CPT	33536
Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using arterial graft(s), single coronary arterial graft	HCPCS	S2205
Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using arterial graft(s), 2 coronary arterial grafts	HCPCS	S2206
Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using venous graft only, single coronary venous graft	HCPCS	S2207
Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using single arterial and venous graft(s), single venous graft	HCPCS	S2208
Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using 2 arterial grafts and single venous graft	HCPCS	S2209
Percutaneous transluminal coronary thrombectomy (List separately in addition to code for primary procedure)	CPT	92973
Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel (List separately in addition to code for primary procedure)	CPT	92981
Percutaneous transluminal coronary balloon angioplasty; each additional vessel (List separately in addition to code for primary procedure)	CPT	92984

Description	Code Type	Code
Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty; each additional vessel (List separately in addition to code for primary procedure)	CPT	92996
Percutaneous transcatheter placement of drug-eluting intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	HCPCS	C9601
Percutaneous transluminal coronary atherectomy, with drug-eluting intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	HCPCS	C9603
Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft (list separately in addition to code for primary procedure)	HCPCS	C9605
Thrombolysis, coronary; by intracoronary infusion, including selective coronary angiography	CPT	92975
Thrombolysis, coronary; by intravenous infusion	CPT	92977
Insertion of drug-eluting coronary artery stent(s)	ICD-9 Proc	36.07
Percutaneous transmyocardial revascularization	ICD-9 Proc	36.34
Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel	CPT	92980
Percutaneous transluminal coronary balloon angioplasty; single vessel	CPT	92982
Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty; single vessel	CPT	92995
Percutaneous transcatheter placement of drug eluting intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch	HCPCS	C9600
Percutaneous transluminal coronary atherectomy, with drug eluting intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch	HCPCS	C9602
Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel	HCPCS	C9604
Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel	HCPCS	C9606
Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel	HCPCS	G0290
Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel	HCPCS	G0291
Other transmyocardial revascularization	ICD-9 Proc	36.32
Other heart revascularization	ICD-9 Proc	36.39

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