1 ABSTRACT

Title

Post-authorization Safety Study Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder: Final Report of the Core Study

Keywords

Cardiovascular events, overactive bladder, mirabegron, antimuscarinic medications

Rationale and background

Astellas obtained marketing authorization in the United States (US) on 28 Jun 2012 and in the European Union (EU) on 20 Dec 2012 for mirabegron to treat overactive bladder (OAB). The Food and Drug Administration (FDA) issued a post marketing requirement (PMR 1898-3) to evaluate risks of cardiovascular (CV) events with mirabegron. The European Medicines Agency (EMA) requested a post authorization safety study (PASS) to assess the CV safety of mirabegron, with a special focus on elderly patients (MEA 001). This PASS was designed to address these concerns. The research effort was organized as a program in multiple populations that used data derived from 5 electronic health care databases in the US and Europe. The studies performed in each database followed the same core protocol, although operational details varied due to the specifics of the different data environments; therefore, site-specific protocols were also developed. CV events (major adverse cardiovascular events [MACE], acute myocardial infarction [AMI], stroke, CV mortality) and all-cause mortality were identified from:

- Direct linkage to registries (Danish National Databases, Swedish National Databases, and Clinical Practice Research Datalink [CPRD]-linked)
- Medical chart adjudication and linkage to the National Death Index (NDI) database (Optum Research Database [ORD] and Humana Database)
- Questionnaires sent to physicians (CPRD-unlinked)

Research question and objectives

The research question for this study was to evaluate the risk of CV events and all-cause mortality associated with mirabegron use.

The primary objectives addressed in this final report were:

1. To estimate and compare the incidence of CV and mortality outcomes within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to antimuscarinic medications (as a group) used in the treatment of OAB. The main outcome of interest was a composite measure of MACE, defined as the first of AMI, stroke, or CV mortality. Additional outcomes of interest included the following individual events: AMI, stroke, CV mortality, and all-cause mortality.
2. To estimate the association described in Objective 1 by patient age (younger than age 65 years, age 65 years and older).

3. To estimate the association described in Objective 1 among patients at high risk for CV events.
4. To estimate the association described in Objective 1 among naïve new users and non-naïve new users of mirabegron or antimuscarinic medications. Naïve new users had no prescriptions or dispensings for an OAB medication in the prior 12 months. Non-naïve new users had a prescription or dispensing for some other OAB medication in the prior 12 months.

The secondary objectives of this study were:

5. To estimate and compare the incidence of MACE, AMI, stroke, CV mortality, and all-cause mortality within *current* exposure to mirabegron and *current* exposure to antimuscarinic medications (as a group) in intervals of time since initiation (i.e., < 60 days, 60 to < 120 days, 120 to < 180 days, ≥ 180 days).
6. To estimate and compare the incidence of MACE, AMI, stroke, CV mortality, and all-cause mortality within categories of recency of use:
    6a. *Recent* exposure to mirabegron vs *past* mirabegron exposure.
    6b. *Current* exposure to mirabegron vs *past* mirabegron exposure.
    6c. *Recent* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group).
    6d. *Current* exposure to antimuscarinic medications (as a group) vs *past* exposure to antimuscarinic medications (as a group).
7. To estimate and compare the incidence of MACE, AMI, stroke, CV mortality, and all-cause mortality across tertiles of cumulative dose (*current* exposure only) of mirabegron.
8. To estimate and compare the incidence of MACE, AMI, stroke, CV mortality, and all-cause mortality across tertiles of cumulative dose (*current* exposure only) of antimuscarinic medications, restricted to the most commonly observed medication in each data source.
9. To estimate and compare the incidence of MACE, AMI, stroke, CV mortality, and all-cause mortality within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to each *individual* antimuscarinic medication (where sample size allows).
10. To estimate and compare the incidence of MACE, AMI, stroke, CV mortality, and all-cause mortality within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to antimuscarinic medications (as a group), stratified by the presence or absence of a history of AMI or stroke.
11. To estimate and compare the incidence of MACE, AMI, stroke, CV mortality, and all-cause mortality within the person-time of *current* exposure to mirabegron and the person-time of *current* exposure to antimuscarinic medications (as a group), restricted

to episodes without current exposure to OAB medications in the past 30 days. This includes naïve new use and non-naïve new use that starts at least 30 days after the end of *current* exposure to an OAB medication.

Study design

This retrospective cohort study included patients exposed to mirabegron or antimuscarinic medications from 01 Oct 2012 through 31 Dec 2018. Exposure to the study drugs, mirabegron and antimuscarinic medications (oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine), was identified using prescriptions or dispensing information as recorded in each database.

The study population consisted of patients who contributed episodes of person-time during new use of medications for the treatment of OAB. A new user of any drug of interest was a patient who received a prescription or dispensing for mirabegron or any antimuscarinic OAB drug during the study period, was at least 18 years of age at the time of the prescription or dispensing, and without a prescription or dispensing for the same specific medication in the previous 12 months. At cohort entry, this definition permitted a person to be either a naïve new user or a non-naïve new user. The predicted probability of starting treatment with mirabegron relative to antimuscarinic medications, conditional on baseline covariates, was estimated to create a propensity score (PS). The cohorts were then formed by PS-matching at a ratio of 1 episode of mirabegron use to 1 comparator episode of antimuscarinic medication use. The PS for each eligible episode was calculated using baseline data for that episode. By updating the covariates included in the PS for each episode contributed by a patient, time-dependent changes in baseline covariates were incorporated into the matching process. This reduced the potential for confounding caused by changes in patient characteristics from one episode to another.

Matched treatment episodes of new use of mirabegron were compared to episodes of new use of antimuscarinic medications. The person-time contributed by the PS-matched mirabegron and antimuscarinic treatment episodes were categorized into *current* exposure (defined as the days' supply in the prescription/dispensing plus a grace period of 50% of the days' supply of the most recent prescription/dispensing), *recent* exposure (defined as the 60 days following the end of *current* exposure), and *past* exposure (defined as all follow-up time after *recent* exposure until censoring or a new prescription/dispensing of the same medication was observed). These person-time categories allowed for the estimation of outcome incidence rates associated with time since treatment in the study population. The main outcome of interest was a composite measure of MACE, defined as the first of AMI, stroke, or CV mortality. Additional outcomes of interest included the following individual events: AMI, stroke, CV mortality, and all-cause mortality. The primary focus was on the incidence of CV outcomes during *current* exposure. In addition to data source-specific analyses, estimates obtained from all data sources were analyzed using a meta-analysis approach.

Setting

This cohort study used 5 data sources and was a collaborative analytic and scientific effort by the following research partners.

- Investigators from the University of Southern Denmark (SDU) led the work involving Danish National Databases.
- Investigators from the Centre for Pharmacoepidemiology, Karolinska Institutet (KI) led the work involving Swedish National Databases.
- Investigators from RTI Health Solutions (RTI-HS) led the work involving the CPRD General Practitioner Online Database (GOLD) and related linkages.
- Investigators from Optum in the US led the work involving the Optum Research Database (ORD).
- Investigators from Humana Healthcare Research (HHR) led the work involving a second US data source, the Humana Database.

Patients and study size, including dropouts

During the accrual period, 896422 mirabegron episodes and 7040463 antimuscarinic medication episodes were identified prior to applying the study inclusion and exclusion criteria. Approximately 90% of the episodes were excluded for various reasons, including age younger than 18 years, having a dispensing of the same drug in the prior 12 months, having prescriptions or dispensings for multiple different OAB medications on the same day, or having prescriptions or dispensings for non-tablet OAB medication formulations. Patients were also excluded if they had less than 12 months of continuous enrollment in the data source, or due to data source-specific administrative reasons.

A total of 178150 mirabegron episodes and 691548 antimuscarinic medication episodes were eligible for PS matching after applying the inclusion and exclusion criteria. Of these, 152026 mirabegron episodes and 152026 antimuscarinic medication episodes were matched to each other in a 1:1 ratio. The numbers of matched OAB medication treatment episodes by data source were as follows: Danish data ($n_m = n_a = 38122$), Swedish data ($n_m = n_a = 44153$), CPRD-linked ($n_m = n_a = 5180$), CPRD-unlinked ($n_m = n_a = 7607$), Optum ($n_m = n_a = 28421$), Humana ($n_m = n_a = 28543$).

Variables and data sources

Pre-specified covariates identified during the baseline period were considered for inclusion in the PS models and included demographics, clinical co-morbidities, treatment history and healthcare utilization variables, defined within each database. The data sources used were the Danish National Databases, Swedish National Databases, CPRD GOLD (linked and unlinked), ORD, and Humana Database.

Results

The study population mainly included women (ranging from 55.1% to 70.9% of matched episodes across data sources), with a median age on the prescription/dispensing date of the

PS-matched OAB treatment episodes ranging from 68 to 73 years across data sources. Users of mirabegron and antimuscarinic medications were similar with respect to CV risk factors, including age, and history of stroke or AMI.

Incidence rates (IR) per 1000 person-years during *current* mirabegron exposure in the combined data sources were 21.99 (95% CI: 20.97, 23.05) for MACE, 5.12 (95% CI: 4.63, 5.64) for AMI, 12.78 (95% CI: 12.00, 13.59) for stroke, 5.67 (95% CI: 5.17, 6.22) for CV mortality, and 34.95 (95% CI: 33.66, 36.28) for all-cause mortality. During *current* antimuscarinic medication exposure, the IRs were 22.71 (95% CI: 21.59, 23.86) for MACE, 5.32 (95% CI: 4.80, 5.89) for AMI, 12.05 (95% CI: 11.25, 12.90) for stroke, 7.09 (95% CI: 6.48, 7.74) for CV mortality, and 41.10 (95% CI: 39.60, 42.65) for all-cause mortality.

For the meta-analysis, hazard ratios (HRs) comparing outcome incidence rates during *current* mirabegron exposure compared to *current* antimuscarinic medication exposure were estimated from *fixed effects* and *random effects* models. Given the similarity in results between these 2 models, *fixed effects* HRs are reported in this abstract. The HRs for MACE, AMI, and stroke ranged from 0.94 to 1.00, and the corresponding 95% CIs included 1. The HRs for CV mortality and all-cause mortality were 0.83 (95% CI: 0.73, 0.95) and 0.80 (95% CI: 0.76, 0.84), respectively. Results among patient episodes at high risk for CV events, stratified by age (< 65 and ≥ 65 years), and among naïve and non-naïve new users were similar to the overall results. The results were also fairly consistent across the range of secondary objective analyses.

Sensitivity analyses suggested no more than a minor influence of potential residual confounding due to inadequately recorded lifestyle factors (smoking, alcohol use, and obesity).

Discussion

Overall, there were no appreciable differences in the incidence of MACE, AMI, and stroke between *current* users of mirabegron and *current* users of antimuscarinic medications. *Current* users of mirabegron experienced a lower risk of CV mortality and all-cause mortality compared to *current* users of antimuscarinic medications. Although our study controlled for several risk factors for CV and mortality outcomes, it is possible that unmeasured risk factors for these specific events differed between users of mirabegron and users of antimuscarinic medications. Examples of such unmeasured risk factors include markers for frailty or social determinants of health.

Conclusions

This study found no higher risk of MACE, AMI, stroke, CV mortality, or all-cause mortality among *current* users of mirabegron as compared to *current* users of antimuscarinic medications. Given the diverse nature of the study population, these study findings may be generalizable to mirabegron users in healthcare systems beyond those included in this study.