1 ABSTRACT

Title

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

Keywords

Cancer, overactive bladder, mirabegron, antimuscarinic medications

Rationale and background

On 28 Jun 2012, Astellas obtained marketing authorization in the United States (US) for mirabegron to treat overactive bladder (OAB). The Food and Drug Administration (FDA) issued a post marketing requirement (PMR 1898-4) to evaluate cancer risks with mirabegron. This post-authorization safety study (PASS) was designed to address the FDA concern. The research effort has been organized as a program in multiple populations that use data derived from 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 developed. For this final report, cancer cases used in the analyses were identified from direct linkage to cancer registries (Danish National Databases, Swedish National Databases, and Clinical Practice Research Datalink (CPRD)-linked), or from medical chart adjudication (Optum Research Database (ORD) and Humana Database) or questionnaires sent to physicians (CPRD-unlinked).

Research question and objectives

The research question for this study was to evaluate cancer risk associated with mirabegron use.

The primary objectives addressed in this final report are:

1. To estimate and compare the incidence of sex-specific composite cancer endpoints (1 for men and 1 for women) among new users of mirabegron and new users of any comparator antimuscarinic medication (as a group) used in the treatment of OAB (referred to as ‘antimuscarinic medications’ throughout), overall and separately for categories of time: person-time in the 1 year following the start of treatment, and person-time in the period more than 1 year following the start of treatment.
2. To perform the analysis described in primary objective 1 with the following modifications:
    - 2a. Stratify by outlier vs non-outlier comparator antimuscarinic medication(s) (with respect to cancer incidence), if present
    - 2b. Stratify by the matching ratio
    - 2c. Exclude bladder and prostate cancer (in men) and bladder cancer (in women)
3. To perform the analysis described in primary objective 1, restricted to patients aged 65 years and older.

4. To estimate and compare the incidence of the 10 individual sex-specific cancers included in the composite cancer endpoints among new users of mirabegron and new users of any comparator antimuscarinic medication, overall and separately for categories of time: person-time in the 1 year following the start of treatment, and person-time in the period more than 1 year following the start of treatment.

For the 1st and 4th primary objectives, sensitivity analyses to examine protopathic bias were conducted by estimating and comparing the incidence in post-treatment initiation intervals: 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, ≥ 24 months.

A series of secondary objectives were evaluated for the sex-specific composite outcomes, overall and separately for categories of time: person-time in the 1 year following the start of treatment, and person-time in the period more than 1 year following the start of treatment.

5. To estimate and compare the sex-specific composite outcomes with the following modifications:

    5a. Stratify by new user status (i.e., naïve new users vs non-naïve new users).

    5b. Exclude immunocompromised patients.

    5c. Censor person-time when an antimuscarinic medication initiator switches to or adds mirabegron, with no censoring if a mirabegron initiator switches to or adds antimuscarinic medication(s).

    5d. Censor person-time when an antimuscarinic medication initiator switches to or adds mirabegron, or a mirabegron initiator switches to or adds antimuscarinic medication(s).

    5e. Stratify by age groups (i.e., 18 to ≤ 44 years, 45 to ≤ 54 years, 55 to ≤ 64 years, 65 to ≤ 74 years, 75 years and older).

6. To estimate and compare the effect of cumulative dose of mirabegron (in tertiles) relative to cumulative dose of the most commonly observed antimuscarinic medication (in tertiles).
7. To estimate and compare the effect of cumulative dose within tertiles of mirabegron dose.
8. To estimate and compare the effect of cumulative dose within tertiles of mirabegron dose, excluding bladder and prostate cancer (in men) and bladder cancer (in women).
9. To estimate and compare the effect of cumulative dose within tertiles of the most commonly observed antimuscarinic medication, excluding bladder and prostate cancer (in men) and bladder cancer (in women).

Study design

The study period for this final analysis was from 01 Oct 2012 through 30 Sep 2018. In a propensity score (PS)-matched cohort study, new users of mirabegron were compared to new users of antimuscarinic medications. Exposure was based on prescription and/or dispensing data and only new users were included. The primary endpoints were 2 sex-specific composite cancer outcomes, defined as the occurrence of any of the individual sex-specific cancers as follows:

Composite endpoint

- The composite endpoint for men included the first occurrence of cancer of the prostate, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin's lymphoma, kidney and renal pelvis, and pancreas.
- The composite endpoint for women included the first occurrence of cancer of the breast, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin's lymphoma, kidney and renal pelvis, corpus uteri, pancreas.

Setting

This cohort study used 5 different 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 Databases.
- Investigators from Optum in the US led the work involving the 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

The total number of OAB medication initiators during the accrual period across all data sources was 3,181,852. Approximately 85% of the patients were excluded for various reasons, including being less than 18 years of age, having a dispensing of the same drug in the prior 12 months, or a dispensing of mirabegron or history of cancer during all available time prior to the index date. Patients were also excluded if they had less than 12 months of continuous enrollment in the data source, and for other site-specific reasons. After applying the exclusion criteria, the remaining 459,610 patients (mirabegron (n_m) = 99,473 and antimuscarinic medications (n_a) = 360,137) were eligible for PS matching and from these, 250,522 were matched (n_m = 80,637 [32%] and n_a = 169,885 [68%]).The numbers of the matched OAB initiators by data source were as follows: Danish data (n_m= 21,815, n_a= 21,815), Swedish data (n_m= 32,283, n_a= 62,838), CPRD-linked (n_m= 2,502, n_a= 7,479), CPRD-unlinked (n_m=3,491, n_a= 10,627), ORD (n_m=9,625, n_a= 28,981), and Humana (n_m= 10,921, n_a= 38,145).

Variables and data sources

Exposure to the study drugs, mirabegron and antimuscarinic medications (oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine), was identified using prescriptions or dispensings information as recorded in each database. 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 (linked and unlinked), ORD, and Humana Database.

Results

PS-matching within each database achieved balance across a range of key measured covariates. From the 250,522 matched initiators of mirabegron and antimuscarinic medications identified across all data sources, 169,594 (68%) were 65 years and older. Within each data source, there was a higher proportion of women than men, ranging from 56% in the Danish database to 74% in Humana (total = 164,336 [66%]).

Results to evaluate heterogeneity of cancer risk across antimuscarinic medications in each data source showed no appreciable heterogeneity of cancer incidence across antimuscarinic medications included in the study. The observed number of dispensings/prescriptions, length of follow-up, and reasons for censoring in the matched mirabegron cohort and the matched antimuscarinic medications cohort, varied across data sources. The median total days supply for mirabegron ranged from 90 days in Humana data to 300 days in the Danish data; for antimuscarinic medications, the median total days supply ranged from 88 days in CPRD-linked data to 210 days in the Danish data. The longest median follow-up time was observed in the Danish data for the mirabegron cohort and was approximately 2.8 years (1,019 days); the shortest median follow-up time was just under one year (334 days) and was observed in the ORD for the antimuscarinic medications cohort.

Across all data sources, a total of 2,750 cancer cases (n_m = 1,219, n_a = 1,531) were observed among women; 3,085 cancer cases (n_m = 1,351, n_a = 1,734) were observed among men. The incidence rates were generally higher for men than women, for both the composite cancer outcomes and for each of the individual cancer outcomes. Incidence rates in the PS-matched cohorts for the composite cancer outcomes (per 1,000 person-years) were 10.09 (95% CI: 9.53, 10.67) and 8.71 (95% CI: 8.28, 9.16) among women, and 21.01 (95% CI: 19.91, 22.15) and 18.99 (95% CI: 18.12, 19.90) among men. Incidence rates were consistently higher in patients aged 65 years and older for both sexes.

Overall, meta-analyses results showed no association between mirabegron use and the risk of cancer, as compared to exposure to antimuscarinic medications, in either men or women. For the composite cancer outcome, all ages, the *fixed effects* overall hazard ratio (HR) was 1.05 (95% CI: 0.98, 1.14) for women and 1.06 (95% CI: 0.98, 1.14) for men. The *fixed effects* overall HR among patients 65 years and older was 1.06 (95% CI: 0.97, 1.16) for women and 0.99 (95% CI: 0.91, 1.07) for men. Results for the *random effects* models were not markedly different. Specific estimates for time since treatment initiation also showed no indication of an association between the use of mirabegron and the risk of cancer, in either men or women.

Results from assessment of the 10 individual cancers in the time intervals of 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, and ≥ 24 months suggested presence of protopathic bias. The highest incidence rates were observed in the first 6 months compared to the later time intervals in both treatment groups, most notably for bladder and prostate cancers. The incidence rates for prostate cancer among men in the mirabegron cohort were 15.67 (95% CI: 13.81, 17.72), 8.65 (95% CI: 7.17, 10.36), 7.04 (95% CI: 5.91, 8.32) and 6.10 (95% CI: 4.98, 7.40), for each of the time intervals, respectively; the corresponding incidence rates for men in the antimuscarinic medications cohort were 13.09 (95% CI: 11.72, 14.58), 7.79 (95% CI: 6.62, 9.12), 6.66 (95% CI: 5.72, 7.71) and 5.16 (95% CI: 4.22, 6.26).

Results from secondary analyses, including assessment of cumulative dose exposure, overall showed no indication of an association between mirabegron use and the risk of cancer, for either men or women. Sensitivity analyses that sought to adjust for (inadequately measured) lifestyle factors such as smoking, alcohol use, and obesity, showed minimal residual confounding of the observed effect estimates.

Discussion

This study provides real world assessment of cancer risk among mirabegron users relative to users of antimuscarinic medications. The study used 5 data sources from 4 countries, providing a wide array of patient characteristics, drug utilization and medical practice patterns. Cancer cases were identified either from direct linkage to cancer registries or confirmed through medical record adjudication or questionnaires sent to physicians.

The patient population included in this final report is substantially larger than was originally projected, given that the person-years of exposure to mirabegron were greater (men: 64,305; women: 120,826) than assumed (men: 20,000; women: 60,000). Follow-up time was up to 5 years for some patients, especially those in the Danish and Swedish databases. In the US data sources, follow-up time was relatively short since ORD and Humana are commercial insurance databases and typical length of follow-up is limited to the time within which patients are enrolled in the health plan. Both of these data sources, however, include Medicare Advantage populations that typically have lower turnover and contribute longer observed follow-up compared to the commercially insured population.

The primary analyses showed no indication of an association between mirabegron use and risk of cancer outcomes, as compared to exposure to antimuscarinic medications, in either men or women. The results were similar in all patients or when restricted to patients age 65 years and older. These findings are consistent with those presented in the interim report of this study. The higher incidence rates for bladder and prostate cancers observed in the first 6 months after treatment initiation suggest the presence of protopathic bias. Although there was some heterogeneity in estimates across data sources for various analyses, and the length of follow-up was somewhat limited for solid tumors, overall the results of this study suggest no association between mirabegron at current use patterns, and risk of a variety of forms of cancer, individually or in aggregate, as compared to antimuscarinic use. Furthermore, there was no association in a range of secondary and sensitivity analyses performed, including short term use, as in the clinical trials that generated the safety concern.

Conclusions

The results from this study suggest no association between mirabegron use and the risk of cancer, as compared to antimuscarinic medication use, in either men or women. Given the diverse nature of the study population, these study findings may be generalizable to the broader population of mirabegron users in real world practice with similar use patterns and health care systems.

Reviewer's Guide

Astellas is providing a Reviewer's Guide [Table 1] to orient the reviewer and to provide general guidance on the approach taken by Astellas concerning the various FDA communications regarding this study.

Table 1 FDA Requests Related to 178-CL-113 Final Report

FDA Communication	FDA Request	Location of Supporting Information
FDA Advice/Information Request Letter dated 14 Dec 2017	For the sensitivity analysis and the use of external adjustment to investigate the impact of residual confounding, describe the source of external data, provide justification on which unmeasured confounder(s) you are aiming to account for by using the external adjustment, and whether there are any met or unmet assumptions (e.g., whether the external data contains the same measures used in the main study and the external population is representative of the main study population).	The impact of adjusting for smoking, alcohol intake and obesity within the CPRD data was examined as well as the impact of a similar adjustment in the other databases per methods described by Schneeweiss, 2006. See 178-CL-113 Final Report [Section 10.4.2 Secondary Analyses Results, Sensitivity Analysis to Investigate the Impact of Residual Confounding]. Annex 4 Table [F0] and [F14]
	Regarding your response to FDA Comment/Recommendation #8: We recommend a weighted Kaplan-Meier plot, not stratified by matching ratio.	Weighted Kaplan-Meier plots for each data source are provided. See 178-CL-113 Final report [Annex 6].
FDA General Advice Letter dated 30 Jan 2018	Your interim analysis using the main study data sources identified roughly 5.7 and 3.9 times higher than expected incidence rates for the composite cancer outcome in males and females, respectively. Discuss in your final study report the potential reasons for the higher than expected incidence rates of the study outcome overall, and the potential reasons for the higher rates seen in males compared to females. Present analytical results by individual cancer types in your final study report.	The 178-CL-113 Final report addresses this request in [Section 11.1] and Annex 4, Tables: [F7_M], [F7_(D,S,CL,CU,O,H)], [F8_M], [F8_(D,S,CL,CU,O,H)]

Table 1 FDA Requests Related to 178-CL-113 Final Report

FDA Communication	FDA Request	Location of Supporting Information
	For the meta analysis, heterogeneity across data sources increased in the secondary analyses and the combined Main and Complementary data sources. Discuss in the final report the effects of heterogeneity on the secondary results from the meta analyses and the results from the combined data sources.	Main (linked) and Complementary (unlinked) data sources were combined for all analyses in the final report since full adjudication of cases identified in the unlinked data sources was conducted. Overall, there was no substantial heterogeneity observed across all the data sources as shown by the I^2 values (<50%) in the meta-analyses tables and the forest plots. See 178-CL-113 Final report [Annex 4], [Annex 5] and [Section 11.1]
	Provide crude hazard ratio (HR) estimates and lists of the covariates adjusted in each individual Cox model in your final study report.	See 178-CL-113 Final report [Section 9.9.5.1 Deviations from the Statistical Analysis Plan]
FDA Advice/ Information Request email dated 23 Feb 2018	For us to adequately assess the interim results with regard chronic mirabegron dosing in the phase 3 pediatric study, please address the following comments as soon as possible. Your interim analysis using the main study data sources identified roughly 5.7 and 3.9 times higher than expected incidence rates for the composite cancer outcome in males and females, respectively. Discuss the potential reasons for the higher than expected incidence rates of the study outcome overall, and the potential reasons for the higher rates seen in males compared to females. Present analytical results by mirabegron dose if available.	On 02 Mar 2018, Astellas submitted a response to the FDA Advice/Information Request email dated 23 Feb 2018 (IND 069416, Serial 660). A copy of Astellas' response is attached to the Reviewer's Guide for ease of reference. See related response above within the "**FDA General Advice Letter dated 30 Jan 2018**" entry above.

Table 1 FDA Requests Related to 178-CL-113 Final Report

FDA Communication	FDA Request	Location of Supporting Information
FDA General Advice Letter dated 21 Aug 2018	We agree with your proposal of not stratifying by matching ratio in your primary and secondary analyses. Consider using weights to accommodate variable matching ratio in the outcome analysis. Otherwise, provide references that adjust for the variable matching ratio through a sandwich estimator without using weights for analyses nor stratifying by matching ratio. Incorporate your revisions to the methods or your justification for use of the sandwich estimator into the protocol and resubmit.	One of the primary analyses for the final report estimated the incidence rates and hazard ratios, stratified by the matching ratio. See 178-CL-113 Final report Annex 4, [Table F4b_M] and [Tables F4b_(S,CL,CU,O,H)]. Unweighted Kaplan-Meier plots stratified by the matching ratio are provided for each data source in [Annex 6].
FDA Advice/Information Request email dated 16 May 2019	Conduct your outcome analysis on the weighted data or stratify the outcome analysis by matched set. You proposed weights that reflect the matching ratio to assess balance after propensity score matching. We believe that the same weights should also be applied to your outcome analysis.	

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