Original Article

Safety and Effectiveness of Mirabegron in Patients with Overactive Bladder in a Real-World Clinical Setting: A Japanese Post-Marketing Study

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Objectives: To provide real-world data on Japanese patients with overactive bladder (OAB) initiating treatment with the \(\beta_3\)-adrenoceptor agonist, mirabegron. This study examined prescribing patterns, adverse drug reaction (ADR) incidence, and treatment effectiveness.

Methods: Full medical histories, including prior/concomitant drug use, were collected before initiating mirabegron treatment. After 12 weeks mirabegron, physicians assessed ADR incidence and treatment effectiveness. Residual urine volume was assessed and patients completed the Overactive Bladder Symptom Score (OABSS) and International Prostate Symptom Score-Quality of Life (I-PSS QoL) surveys at Baseline and 12 weeks. Data were collected between April 2012 and July 2014.

Results: Of 9795 OAB patients (46.8% male; 80.8% \(\geq\) 65 years), 71.7% had coexisting disease [notably benign prostatic hyperplasia (BPH, 32.4%), hypertension (31.9%), and diabetes mellitus (9.4%)] and 53.4% reported concomitant drug use (27.8% \(\alpha_1\)-antagonists, 6.3% anticholinergics). The incidence of total ADRs was 6.07% [including constipation (0.97%), thirst (0.47%), and dysuria (0.44%)], of serious ADRs, 0.21%, of cardiovascular ADRs, 0.48% and of urinary retention, 0.31%. Incidence of total ADRs in patients with concomitant cardiovascular disease was 10.09% and of those related to urinary retention in men with untreated BPH, 0.88%. After 12 weeks treatment, physicians judged mirabegron as “effective” in 80.7% of patients, 63.6% of patients achieved the three-point minimal clinically important change from Baseline in the mean OABSS, and the I-PSS QoL decreased significantly from Baseline (\(-2.1 \pm 1.77\); \(P < 0.001\)).

Conclusions: In the clinical setting, mirabegron is well tolerated, with no unanticipated ADRs, and is an effective treatment for Japanese patients with OAB.

Key words \(\beta_3\)-adrenoceptor agonist, mirabegron, overactive bladder, post-marketing survey

1. INTRODUCTION

Overactive bladder (OAB) is a symptom complex defined as “having urgency, usually with frequency and nocturia, with or without urge urinary incontinence.” Overactive bladder is a chronic condition, the prevalence of which increases with age, and it can have a substantial impact on quality of life. OAB is thought to affect more than 400 million people worldwide and it has been estimated that 12.4% of the population in Japan experience the symptoms of OAB. Antimuscarinic agents are the most commonly prescribed therapeutic agents for the treatment of OAB, but bothersome side-effects, such as dry mouth and constipation, can result in low patient adherence. Mirabegron is a \(\beta_3\)-adrenoceptor agonist, first approved for the treatment of OAB in Japan in 2011. It has since been approved in other regions including the USA, Canada, and Europe. Mirabegron is thought to alleviate OAB symptoms by eliciting \(\beta_3\)-adrenoceptor–dependent relaxation of the bladder detrusor muscle, thus increasing bladder capacity without affecting voiding. Because of its different mechanism of action, mirabegron is well tolerated and patients experience fewer undesirable anticholinergic side effects than with antimuscarinic agents. Mirabegron is an alternative therapeutic option for patients with OAB, particularly for those in whom antimuscarinic agents are contraindicated.

Since its market release in Japan, clinical data on the use of mirabegron has been limited to that collected in the relatively controlled environment of clinical trials. However, as mirabegron will be administered to a wide variety of patients in real-world clinical use (notably the elderly or those with concomitant diseases and/or}
pharmacotherapies), this drug use-results study was conducted to further understand the safety, efficacy, and appropriate use of mirabegron in patients with OAB receiving mirabegron in a routine clinical setting. Specifically, this report focuses on the safety and efficacy of mirabegron treatment, including the incidence of adverse drug reactions (ADRs) and potentially associated risks for patients with OAB and concomitant lower urinary tract obstruction or cardiovascular (CV) abnormalities.

2. METHODS

The study protocol was performed in accordance with the standards for Good Post-Marketing Study Practice (GPSP of the Japanese Ministry of Health, Labour and Welfare).11 The study is registered with clinicaltrials.gov as NCT01919047.

2.1. Survey methods and participants

Patients were registered and data collected via the internet-based post-marketing survey data collection system, PostMaNet. Male and female patients diagnosed with OAB by the attending physician (based on their daily clinical medical care with or without interventional investigations for the present survey), who had been prescribed mirabegron for OAB symptoms urgency, frequency, nocturia, with or without urgency incontinence, and who had not been previously treated with mirabegron, were eligible to participate in the study. Within 14 days of the start of mirabegron treatment (not including the start day), physicians registered each patient. Physicians entered survey data of all registered patients (including patients discontinued or withdrawn) at end of the 12-week observation period or at discontinuation.

2.2. Patient assessments

Patient characteristics collected included sex, presence/absence of pregnancy/lactation (including during the observation period), date of birth, weight, inpatient/outpatient status at baseline, duration of OAB, concurrent diseases (presence/absence, name of the disease, severity of symptoms for hypertension), medical history (presence/absence, name of the disease), and prostate volume (male only).

Prior and concomitant drug use, notably drugs prescribed for OAB (other than mirabegron), were recorded. Prior drug use included those medications used in the 4 weeks prior to the start of mirabegron treatment.

Presence or absence of adverse events (AEs) (including ADRs and abnormal laboratory values or other test values) that occurred during treatment with mirabegron or after the completion of treatment were recorded. The incidence of ADRs was evaluated after 12 weeks of mirabegron treatment or at discontinuation. All ADRs collected, including those reported in discontinued/dropout patients, were summarized and coded using system organ class (SOC; number of patients) and preferred term (PT; number of events) of Japanese MedDRA version 17.1.

Residual urine volume was measured at baseline and after 12 weeks of mirabegron treatment (or at discontinuation). Patients completed the OABSS and the International-Prostate Symptom Score Quality of Life (I-PSS QoL) instruments at baseline and at week 12 (or at time of discontinuation). Physicians evaluated the change from baseline in OAB symptoms at week 12 (or at the time of discontinuation) as “effective” or “ineffective.” If symptoms were not evaluable, reasons for considering them not evaluable were recorded.

2.3. Statistical analysis

The planned sample size in this study was 10,000 patients to allow for the detection of ADRs occurring at lower frequency. Wilcoxon signed-rank test was used for testing the difference from baseline in values during the observation period.

3. RESULTS

3.1. Patient disposition and baseline characteristics

The study was conducted from April 2012 to July 2014. Survey data were collected from 10,688 patients across 1111 medical institutions. As shown in Figure 1, of the 10,688 patients registered, 9,795 were included in the safety analysis set (SAF) and 893 were excluded (867 did not visit a medical institution after the first dose of mirabegron, eight outside the contract period, seven failed to meet the registration criteria, six outside the registration period, five who did not receive mirabegron, and three who refused to cooperate in confirmation of ADRs). Of those included in the SAF population, 9,792 patients diagnosed with OAB and eligible for efficacy assessment by the attending physician, were included in the efficacy analysis set. The 4153 patients from the efficacy analysis set who met the OABSS definition of OAB at baseline (OABSS questionnaire score ≥2 points and total OAB score ≥3 points), who received mirabegron in accordance with the dosing regimen, and who completed the OABSS at baseline and week 12 (including at the time of discontinuation) without missing values, were included in the OABSS analysis set.

During the 12-week observation period, 28.9% (n = 2829) of those in the SAF (n = 9795) discontinued or were withdrawn from treatment (n = 1636, 16.7%) or did not complete medical visits (n = 1192, 12.2%). Reasons for discontinuation/withdrawal were persistent or aggravated symptoms (n = 690, 7.0%), ADRs (n = 402, 4.1%), patient’s request (excluding ADRs [n = 333, 3.4%]), symptom remission (n = 263, 2.7%), and other reasons (n = 52, 0.5% [including duplications]).

Demographic and baseline patient characteristics are summarized in Table 1. Of the SAF population, 46.8% of patients were men, the mean age was 72.3 ± 10.93 years old, all patients (with one exception) were ≥15 years old, 80.8% of patients were ≥65 years old, and 48.8% were ≥75 years old. Of the men, the mean prostate volume...
was 28.386 ± 17.3225 mL and 306 patients (6.7% of total population) had a prostate volume >50 mL. Regarding OAB status, 68.8% of patients had been diagnosed with OAB for longer than 3 months; 17.5, 55.1, and 14.0% had OABSS of mild, moderate, and severe, respectively; and patients were classified as “DRY” or “WET” (based on presence/absence of incontinence) in 25.0 and 61.8% of cases, respectively.

Patients with concurrent diseases accounted for 7027 (71.7%) of the SAF \( (n = 9795) \). The major concurrent diseases (reported in ≥5%) were benign prostatic hyperplasia (BPH; \( n = 3176 \), 32.4% of SAF population and 69.2% of men), hypertension \( (n = 3124, 31.9\%) \), diabetes mellitus \( (n = 925, 9.4\%) \), and hyperlipidemia \( (n = 885, 9.0\%) \). Furthermore, 2619 patients (26.7%) had a medical history and 1491 patients (15.2%) had received prior medications for OAB (Table 2).

Patients with baseline residual urine volume of <25 mL accounted for 47.5% \( (n = 4648) \) of the population, although there were 141 patients (1.4%) whose baseline residual urine volume was >100 mL (Table 3). Patient histories included prior and concurrent drug usage. Of the SAF \( (n = 9795) \), 5228 patients (53.4%) reported concomitant drug use. Principal drug categories reported by ≥3% of patients included \( \alpha_1 \)-antagonists \( (n = 2720, 27.8\%) \), anticholinergic agents \( (n = 621, 6.3\%) \), and 5-α-reductase inhibitors \( (n = 327, 3.3\%) \). Specified drugs reported by ≥2% of patients included amlodipine besylate \( (n = 495, 5.1\%) \), magnesium oxide \( (n = 215, 2.2\%) \), and aspirin \( (n = 195, 2.0\%) \).

### 3.2. Treatment status

The initial daily dose of mirabegron was 25 mg for 14.5% \( (n = 1419) \), 50 mg for 85.5% \( (n = 8375) \), and 100 mg (unapproved dose) for one patient. The mean daily dose during the treatment period was 25 mg for 11.2% \( (n = 1093) \), >25 mg and <50 mg for 3.8% \( (n = 376) \), and 50 mg for 84.8% \( (n = 8308) \).

### 3.3. Incidence of adverse drug reactions (ADRs)

Of the 9795 patients in the SAF, 682 ADRs were reported in 595 patients. The most common ADRs were constipation (95 patients, 0.97%), increased residual urine volume (70 patients, 0.71%), thirst (46 patients, 0.47%), dysuria (43 patients, 0.44%), and urinary retention (30 patients, 0.31%; Table 2). Of the 682 ADRs, 25 serious ADRs were reported in 21 patients (Table 4).

Urinary retention ADRs were reported in 30 patients (including 10 patients reporting either “residual urine” or “a feeling of residual urine”), of whom 21 were men (including 18 [71.4%] ≥75 years old) and 9 were women (including 6 [66.7%] ≥75 years old). Of the 20 patients with urinary retention ADRs other than “residual urine” or “a feeling of residual urine,” 11 required urethral catheterization. All men reporting urinary retention ADRs had BPH and 16 (76.2%) were receiving either \( \alpha_1 \)-antagonists or a 5-α-reductase inhibitor. The remaining five patients (23.8%) had not been treated for BPH.

Of the 4588 men in the SAF, 69.2% (3176) reported having BPH, of whom 20% (569 patients) were untreated. The incidences of ADRs in men with BPH related to lower
| Characteristic                              | Patients, n (%) |
|--------------------------------------------|-----------------|
| Patients in the safety analysis set (SAF)† |                 |
| Male                                       | 4588 (46.8)     |
| Prostate volume                            |                 |
| <20 mL                                     | 994 (21.7)      |
| ≥20 mL, <30 mL                             | 977 (21.3)      |
| ≥30 mL, <40 mL                             | 569 (12.4)      |
| ≥40 mL, <50 mL                             | 287 (6.3)       |
| ≥50 mL                                     | 306 (6.7)       |
| Unknown                                    | 1455 (31.7)     |
| Female                                     | 5207 (53.2)     |
| No pregnancy/lactation                     | 5207 (100)      |
| Pregnancy/lactation                        | 0               |
| Age                                        |                 |
| Up to 54 years                             | 699 (7.1)       |
| 55–64 years                                | 1181 (12.1)     |
| 65–74 years                                | 3131 (32.0)     |
| 75–84 years                                | 3945 (40.3)     |
| 85 years or older                          | 839 (8.6)       |
| Body weight                                |                 |
| Summary statistics                         |                 |
| n                           | 4358            |
| Mean ± SD                                  | 57.0 ± 10.908   |
| Unknown                                    | 5437 (55.5)     |
| BMI                                        |                 |
| Summary statistics                         |                 |
| n                           | 4175            |
| Mean ± SD                                  | 23.06 ± 6.668   |
| Unknown                                    | 5620 (57.4)     |
| Patient classification                     |                 |
| Inpatient                                  | 100 (1.0)       |
| Outpatient                                 | 9695 (99.0)     |
| OAB duration                               |                 |
| <3 months                                  | 2129 (21.7)     |
| ≥3 months, <1 year                         | 2162 (22.1)     |
| ≥1 year, <3 years                          | 2384 (24.3)     |
| ≥3 years                                   | 2194 (22.4)     |
| Unknown                                    | 926 (9.5)       |
| OAB severity‡                              |                 |
| Mild                                       | 1716 (17.5)     |
| Moderate                                   | 5395 (55.1)     |
| Severe                                     | 1374 (14.0)     |
| Unknown                                    | 1310 (13.4)     |
| DRY/WET classification§                    |                 |
| Dry                                        | 2450 (25.0)     |
| Wet                                        | 6055 (61.8)     |
| Unknown                                    | 1290 (13.2)     |

† Patients who received ≥1 dose of mirabegron. ‡ Severity of total OABSS at baseline. Mild (0, 1, 2, 3, 4, or 5), moderate (6, 7, 8, 9, 10, or 11), and severe (12, 13, 14, or 15). §DRY group: OABSS Question 4 was 0 points at baseline. WET group: OABSS Question 4 was ≥1 point at baseline. BMI, body mass index; OAB, overactive bladder; OABSS, Overactive Bladder Symptom Score.

urinary tract obstruction, either treated and untreated for BPH, respectively, were: dysuria 0.77% (20 of 2588 patients) and 0.70% (4 of 569 patients); urinary retention (including residual urine, etc.) 0.62% (16 of 2588 patients) and 0.88% (5 of 569 patients); decreased urine flow 0 and 0.18% (1 of 569 patients); for increased residual urine volume, 1.31% (34 of 2588 patients) and 0.88% (5 of 569 patients) (Table 5).

In 3739 patients in the SAF for whom residual urine volumes were measured at both baseline and week 12 (including at time of discontinuation), the mean residual urine volume was 21.101 ± 29.6834 mL and 22.409 ± 44.2820 mL at baseline and week 12 (including at the time of discontinuation), respectively. The mean change from baseline to week 12 (including at time of discontinuation) was −48.811 ± 97.3733 mL, and was statistically significant (P < 0.001).

Of the SAF, 674 patients (6.9%) had concurrent CV disease. The total incidence of ADRs in this population was 10.09%, compared with 5.79% in the remaining 8965 patients without concurrent CV disease. During the study period, a total of 50 CV ADRs (including adverse events coded in SOC as cardiac disorders, vascular disorders, and investigations) were reported in 47 patients in the total SAF (incidence 0.48%). CV ADRs reported during the study period included palpitations (17 events), hypertension (nine events), tachycardia (five events), increased blood pressure (four events), hot flush and cardiac failure (three events each), arrhythmia (two events), supraventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, heart rate increased,
deep vein thrombosis, pallor, and N-terminal prohormone brain natriuretic peptide increased (1 event each; Table 6).

A total of two ADRs related to increased intraocular pressure were reported in two patients (incidence <0.1%). In one patient, intraocular pressure was increased and in another, serious case, previously diagnosed glaucoma worsened. A causal relationship with mirabegron cannot be excluded for either case.

3.4. Efficacy

Of the 9792 patients in the efficacy analysis set, efficacy was evaluated by the attending physician at end of treatment or discontinuation in 9394 patients (398 patients were “not evaluable”). Mirabegron treatment was reported to be “effective” in 7582 patients (80.7%) and “ineffective” in 1812 patients (19.3%).

As shown in Table 7, the mean total OABSS ± standard deviation (SD) for the OABSS analysis set (n = 4153) was 9.0 ± 2.53 at baseline, and 5.3 ± 3.25 at end of treatment, thus resulting in a statistically significant change in the total score of −3.7 ± 3.11 (P < 0.001). This change was greater than the mean clinically important change (MCIC) for the total OABSS (defined as a decrease of three points of the total score). The mean total OABSS at baseline for the efficacy analysis set was 8.3 ± 3.02 and was similar to that of the OABSS analysis set. In terms of individual patient outcomes, 2641 patients (63.6%) in the OABSS analysis set achieved the MCIC during their treatment. Furthermore, significant changes were observed for all four OABSS subscores. For the I-PSS QoL score, the mean score ± SD was 5.0 ± 0.93 at baseline, and 2.8 ± 1.61 at end of treatment, resulting in a statistically significant change of −2.1 ± 1.77 (P < 0.001) for the population over the course of treatment.

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**TABLE 2.** Concurrent diseases and prior OAB medication

| Patients, n (%) |
|----------------|
| Patients in safety analysis set (SAF)† 9795 (100) |
| Concurrent No 2612 (26.7) |
| Concurrent disease Yes 7027 (71.7) |
| Concurrent disease present at ≥3% |
| Benign prostatic hyperplasia (males only) 3176 (32.4) |
| Hypertension 3124 (31.9) |
| Grade I 1499 (15.3) |
| Grade II 221 (2.3) |
| Grade III 20 (0.2) |
| Unknown 1384 (14.1) |
| Diabetes mellitus 925 (9.4) |
| Hyperlipidemia 885 (9.0) |
| Constipation 396 (4.0) |
| Insomnia 379 (3.9) |
| Glaucoma 309 (3.2) |
| Osteoporosis 304 (3.1) |
| Angina pectoris 297 (3.0) |
| Arhythmia 298 (3.0) |
| Prostate cancer 292 (3.0) |
| Cardiovascular disease‡ 674 (6.9) |
| Unknown 156 (1.6) |
| Concurrent No 9271 (94.7) |
| Concurrent disease excluded for OAB diagnosis Yes 524 (5.3) |

†Patients who received ≥1 dose of mirabegron. ‡Number of patients with cardiovascular disease including angina pectoris or arrhythmia (duplicate summarization). OAB, overactive bladder.

**TABLE 3.** Residual urine volume and concomitant medication at baseline

| Patients, n (%) |
|----------------|
| Patients in safety analysis set (SAF)† 9795 (100) |
| Residual urine volume Mean (SD) 20.021 (28.66) |
| Summary statistics (mL) n 6662 |
| <25 mL 46 (4.7) |
| ≤25 mL, >25 mL 1194 (12.2) |
| ≤50 mL, >50 mL 679 (6.9) |
| ≤100 mL, >100 mL 141 (1.4) |
| Unknown 3133 (32.0) |

Concomitant medication No 4267 (43.6)
Yes 5228 (53.4)
Unknown 300 (3.1)

†Patients who received ≥1 dose of mirabegron. SD, standard deviation.

**TABLE 4.** Incidence of adverse drug reactions

| Incidence of ADR§ Patients, n (%) |
|----------------|
| Patients in the safety analysis set (SAF) § 9795 (100) |
| Any adverse reaction, n (%) 595 (6.07) |
| Any serious adverse reaction, n (%) 21 (0.21) |
| Common adverse reactions present at 0.1% or higher |
| Constipation 95 (0.97) |
| Residual urine volume increased 70 (0.71) |
| Thirst§ 46 (0.47) |
| Dysuria 43 (0.44) |
| Urinary retention 30 (0.31) |
| Dizziness 27 (0.28) |
| Abdominal discomfort 24 (0.25) |
| Cystitis 24 (0.25) |
| Diarrhea 22 (0.22) |
| Nausea 18 (0.18) |
| Pruritus 12 (0.12) |
| Headache 10 (0.10) |
| Urticaria 10 (0.10) |

§Japanese MedDRA version 17.1. †Patients who received ≥1 dose of mirabegron. §The incidence of the ADR “Thirst” does not include the incidence of patients reporting the ADR “Dry Mouth”. Dry Mouth was reported in 8 patients (0.08%). ADRs, adverse drug reactions.
TABLE 5. Incidence of ADRs related to urinary retention as a function of benign prostatic hyperplasia treatment status

| BPH status | With BPH | No BPH | BPH unknown | Total |
|------------|----------|--------|-------------|-------|
| BPH treatment status | Yes | No | Unknown | — | — | — |
| Patients, n | 2588 | 569 | 19 | 1364 | 48 | 4588 |
| Patients with ADRs, n | 170 | 35 | 1 | 66 | 3 | 275 |
| ADRs, n | 191 | 38 | 2 | 74 | 3 | 308 |
| Incidence of ADRs | 6.57 | 6.15 | 5.26 | 4.84 | 6.25 | 5.99 |

ADRs by PT†

| ADRs by PT† | Incidence of ADRs by PT, events (%) |
|-------------|-----------------------------------|
| Dysuria     | 20 (0.77) 4 (0.70) 0 4 (0.29) 0 28 (0.61) |
| Urinary retention | 16 (0.62) 5 (0.88) 0 0 0 21 (0.46) |
| Decreased urine flow | 0 1 (0.18) 0 0 0 1 (0.02) |
| Residual urine volume increased | 34 (1.31) 5 (0.88) 0 8 (0.59) 0 47 (1.02) |

†Japanese MedDRA version 17.1. ADRs, adverse drug reactions; BPH, benign prostatic hyperplasia; PT, preferred term.

TABLE 6. Incidence of cardiovascular adverse drug reactions

| Concurrent CV disease | Yes | No | Unknown | Total |
|-----------------------|-----|----|---------|-------|
| Patients in SAF†, n   | 674 | 8965 | 156 | 9795 |
| Patients with ADRs, n | 68 | 519 | 8 | 682 |
| ADRs, n               | 79 | 593 | 10 | 682 |
| Incidence of ADRs (%) | 10.09 | 5.79 | 5.13 | 6.07 |

ADRs by PT‡

| ADRs by PT‡ | Incidence of ADRs by PT, events (%) |
|-------------|-----------------------------------|
| Cardiac disorders | 1 (0.15) 1 (0.01) 0 2 (0.02) |
| Heart failure | 2 (0.30) 0 1 (0.64) 3 (0.03) |
| Palpitations  | 2 (0.30) 15 (0.17) 0 17 (0.17) |
| Supraventricular extrasystoles | 1 (0.15) 0 0 1 (0.01) |
| Tachycardia   | 1 (0.15) 3 (0.03) 1 (0.64) 5 (0.05) |
| Ventricular tachycardia | 1 (0.15) 0 0 1 (0.01) |
| Vascular disorders | 1 (0.15) 8 (0.09) 0 9 (0.09) |
| Palor         | 0 1 (0.01) 0 1 (0.01) |
| Deep vein thrombosis | 0 1 (0.01) 0 1 (0.01) |
| Hot flush     | 1 (0.15) 2 (0.02) 0 3 (0.03) |
| Investigations§ | 1 (0.15) 3 (0.03) 0 4 (0.04) |
| Blood pressure increased | 0 1 (0.01) 0 1 (0.01) |
| ECG prolonged QT | 1 (0.15) 0 0 1 (0.01) |
| Heart rate increased | 0 1 (0.01) 0 1 (0.01) |
| N-terminal brain natriuretic prohormone increased | 0 1 (0.01) 0 1 (0.01) |

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The rate of OAB disease severity was examined. A total OABSS score of 0–5 was classified as “mild,” 6–11 as “moderate,” and 12–15 as “severe.” The relative percentages of patients experiencing mild, moderate, and severe OAB, respectively, were 7.8, 73.6, and 18.6% at baseline and 58.0, 37.1, and 5.0% at end of treatment (Fig. 2). The proportion of patients with mild symptom severity increased from 7.8 to 58.0%. A more detailed analysis of the relative proportion of patients responding to each OABSS subscale (three-point scale for daytime frequency, four-point scale for nocturia, and six-point scales each for urgency and urge incontinence), revealed that a greater proportion of patients experienced milder symptoms for each category after treatment with mirabegron (Fig. 3). Finally, in the distribution of severity of I-PSS QoL “mild” (score of 0 or 1), “moderate” (score of 2–4), and “severe” (score of 5 or 6) accounted for 0.3, 25.6, and 74.1%, respectively, at baseline and 20.4, 61.3, and 18.3%, respectively, at week 12 (including at the time of discontinuation; Fig. 4). The proportion of patients with mild/moderate symptoms was higher at week 12, including at the time of discontinuation (81.7%), than at baseline (25.9%).

4. DISCUSSION

Mirabegron is currently the only β3-adrenoceptor agonist approved for the treatment of OAB. Although there is a plethora of data available from the clinical trials, there is currently relatively little, real-world clinical data available for mirabegron. The study results presented here from a real-world population of nearly 10 000 patients with OAB did not raise any safety issues that were not already
detected in registration trials (e.g., lower urinary tract obstruction or CV abnormalities). The major differences in patient baseline characteristics in this study in comparison with those in Japanese clinical studies\textsuperscript{13,14} included higher proportions of male patients, elderly patients, and patients with a medical history, and a lower proportion of patients who received prior OAB therapies. Additionally, this real-world population included patients typically excluded from the clinical studies (e.g., patients with concurrent CV disease, concurrent glaucoma, and patients with residual urine volume of \geq 100 mL).

The overall incidence of ADRs within the SAF population was 6.07% and with the exception of pruritus, all reported reactions were described in the domestic clinical trials.\textsuperscript{13–15} Despite the large patient population, no events requiring extra caution were detected. ADRs related to lower urinary tract obstruction (including residual urine and a feeling of residual urine) occurred more frequently among the study population presented here compared with the patients included in domestic phase III clinical trials.\textsuperscript{13} This finding may be explained by the fact that 46.8% of the participants were men, as opposed to 15.7% in the domestic phase III study. In this study, two-thirds of ADRs related to lower urinary tract obstruction occurred in men, and a majority of whom had concurrent BPH. Typically a limited number of men enroll in clinical studies, and those with clinically relevant lower urinary tract obstruction diseases (BPH, etc.) are excluded.

Several studies regarding mirabegron for patients with lower urinary tract symptoms accompanied by bladder outlet obstruction or BPH have been reported. For example, urodynamic studies involving men with lower urinary tract obstruction demonstrated that mirabegron treatment was non-inferior to placebo in maximum urinary flow rate (Qmax) and detrusor pressure at Qmax (Pdet Qmax)\textsuperscript{16} while no effects on post-void residual volume (PVR). Qmax and PdetQmax were reported for Japanese men with persistent OAB symptoms receiving mirabegron add-on therapy after tamsulosin treatment.\textsuperscript{17} However, in a study of mirabegron add-on therapy to tamsulosin for treatment of OAB systems in men with benign prostatic obstruction, Ichihara and colleagues reported a significant increase in PVR at end of treatment in the tamsulosin and mirabegron combination group compared with the tamsulosin monotherapy group.\textsuperscript{18} While the authors identified no baseline factors that would predict increased PVR, it is of note that mean patient age in this study was 10 years greater than that of the patients in the mirabegron study.\textsuperscript{16}

Here we focused on the potential risk of urinary retention as there is relatively limited information about this issue despite the abundance of patients with OAB and lower urinary tract obstruction in clinical settings. Firstly, 21 of 30 patients with urinary retention ADRs were men with concurrent BPH complications, 23.8% of whom were untreated for BPH.

Furthermore, of the 3176 patients with BPH, 2588 patients (81.5%) also received treatment specific for BPH. The incidence of ADRs related to urinary retention as a function of BPH treatment status revealed a greater tendency for ADRs in patients whose BPH was untreated. This point was considered to be one of the principal causes for the incidence of urinary retention observed in this study.
In addition to concurrent BPH, age appeared to be related to an increased incidence of urinary retention. Indeed, the mean age of the study population was 72.3 ± 10.93 and 71.4% of male and 66.7% of female patients who experienced urinary retention were ≥75 years old. Among the principal ADRs that were more prevalent in patients ≥75 years (n = 4784) compared with patients ≤74 years of age (difference in incidence that was 0.1% or higher) were increased residual urine volume (n = 40, 0.84%), thirst and dysuria (n = 25, 0.52% each), dizziness (n = 22, 0.46%), urinary retention (n = 21, 0.44%), cystitis (n = 15, 0.31%), and urinary tract infection (n = 6, 0.13% [data not shown]).

The incidence of ADRs in patients with bladder outlet obstruction had a tendency to increase with age. Although prevalence of OAB increases with age, it has also been reported that the prevalence of a disease state known as detrusor hyperactivity with impaired contractile function (DHIC), in which bladder contractile function decreases leading to incomplete emptying and, in some cases, chronic urinary retention, also increases in elderly patients. This finding suggests that the bladder conditions in the elderly, other than OAB, may have affected the results in this study.

While the overall incidence of ADRs related to urinary retention in this study was not high (0.31%), we believe that the results suggest that voiding symptoms should be monitored when prescribing mirabegron to patients ≥75 years old or with untreated BPH.

Mirabegron is a selective β3-adrenoceptor agonist. As all three subclasses of β-adrenoceptors are expressed in smooth muscle tissue and the heart, CV adverse events were monitored closely during the mirabegron registration trials. In this study 674 patients (6.9%) in the SAF had concurrent CV disease. The incidence of CV ADRs was 0.48% (50 ADRs reported in 47 of 9795 patients of the SAF) and thus did not exceed the incidence of CV ADRs of 1.85% (7 of 379 patients) reported in the Japanese phase III trials. The CV risks associated with mirabegron use were also evaluated in a pooled analysis of three international phase III trials, in which it was concluded that the incidence of CV adverse events was acceptable and no clinically relevant changes in vital signs were revealed. To investigate this topic further, a separate study has been conducted focusing on CV ADRs in Japanese patients receiving mirabegron for OAB in a...
clinical setting and who have a history of or concurrent CV disease (NCT02570035, publication in preparation).

Finally, this study also provides information about the efficacy of mirabegron in a real-world clinical setting. At the end of treatment, 80.7% of physicians judged mirabegron to be effective. In addition, mean OABSS total score decreased by 3.7 ± 3.11 points (P < 0.001) from baseline to end of treatment, exceeding the MCIC, and significant changes in the I-SSS QoL (−2.1 ± 1.77, P < 0.001) were revealed. Further analysis of symptom severity and individual symptom changes (OABSS/I-PSS QoL severity and OABSS subscores) revealed that, in all cases, patients reported milder symptoms after mirabegron treatment.

In this survey elderly patients were present at a higher percentage than in the clinical studies, and as the Japanese population is aging more rapidly than other populations worldwide, a subgroup analysis by age is planned in order to further explore the safety and efficacy of mirabegron in the elderly.

A potential limitation to the study is that it was based on a survey of real-world patients and therefore was not placebo controlled.

5. CONCLUSION

In the real-world clinical setting, mirabegron is well tolerated with no unanticipated ADRs and is an effective treatment for Japanese patients with OAB.

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Disclosure

Authors are employees of Astellas Pharma Inc.

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