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ORIGINAL ARTICLE

Three-year safety, efficacy and persistence data following the daily use of mirabegron for overactive bladder in the clinical setting: A Japanese post-marketing surveillance study*

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Objective: The aim of this study was to report the final 3-year results from a surveillance study evaluating the safety, efficacy, and persistence of mirabegron for treating overactive bladder (OAB) symptoms.

Methods: Patients who had started mirabegron for the treatment of urinary urgency, daytime frequency, and urgency urinary incontinence symptoms associated with OAB were followed for 3 years. Adverse drug reactions (ADRs), residual urine volume measurements, OAB symptoms, Overactive Bladder Symptom Scores (OABSS), and treatment discontinuations were evaluated prospectively. Persistence was estimated using the Kaplan–Meier method.

Results: Of the 1138 patients included in the study (mean ±SD age: 71.9 ± 11.0 years; 574 [50.4%] women), 97 (8.52%) experienced 109 ADRs, with the incidence of ADRs decreasing over time (<1 year: 1.34%–2.37%; ≥1–<2 years: 0.45%–1.60%; ≥2–<3 years: 0.29%–1.10%; 3-monthly interval data). No significant increases in residual urine volume were observed. The investigators considered mirabegron to be an effective treatment for 842 of 1082 (77.8%) patients. Significant decreases in OABSS were reported throughout ($P < 0.001$), and 321 (65.1%) patients achieved a minimal clinically important change (MCIC) in OABSS. Most patients who achieved an MCIC within ≤1 year continued to maintain an MCIC throughout the study. Treatment persistence rates after 1, 2, and 3 years of mirabegron treatment were 65.8%, 52.9%, and 46.7%, respectively.

Conclusion: Over 3 years, mirabegron was well tolerated and no cumulative events or delayed ADRs were observed. Mirabegron was an effective treatment with early improvements in OABSS being maintained throughout the treatment period. High persistence was observed after the use of mirabegron.

KEYWORDS

efficacy, mirabegron, overactive bladder, persistence, safety

1 | INTRODUCTION

Antimuscarinics remain the principal therapeutic options for treating patients with overactive bladder (OAB) symptoms.[1] This is despite the fact that they are associated with specific anticholinergic side effects, including dry mouth and constipation,[2] which may affect quality of life[3] and treatment persistence.[4] The β₃-adrenoreceptor agonist mirabegron has a different mechanism of action from antimuscarinics,[5,6] which may circumvent the adverse effects associated with antimuscarinic therapy. The efficacy and safety of ≤12 weeks of treatment with mirabegron have been demonstrated in several Phase III trials and post-marketing studies involving patients with OAB symptoms.[7–10] However, owing to the

*This study is registered with Clinicaltrials.gov (ID: NCT01901120).

chronic nature of OAB, sustained pharmacological therapy is required to achieve effective symptom control and positive health outcomes.[4]

Maintenance of the efficacy and safety of mirabegron over a 1-year treatment period has been demonstrated in a Phase III study involving 204 Japanese patients with OAB symptoms.[11] However, mirabegron therapy is administered to a variety of patients in the real-world setting and prolonged treatment may be associated with specific cumulative or delayed unwanted events, or may have an additive effect on the incidence of adverse drug reactions (ADRs). There are also concerns that the continued effectiveness of OAB medication may be diminished because β-adrenoreceptors can potentially become desensitized after prolonged exposure to agonists.[12] If desensitization occurs, it can entail receptor protein phosphorylation, signaling pathway uncoupling, receptor internalization, and long-term gene expression regulation involving the receptor and signaling pathway proteins.

In addition to long-term safety and efficacy, patient persistence with OAB medication can substantially affect the therapeutic outcomes achieved. A previous report indicated that persistence with OAB medication is lower than with treatments used to treat other chronic diseases.[13] However, that study only evaluated the persistence with and adherence to antimuscarinic OAB therapy. Several studies conducted in Japan and elsewhere have suggested that increased persistence can be achieved with mirabegron than with antimuscarinic therapy.[14–17] However, these studies only involved a maximum follow-up period of 1 year and did not investigate the reasons for treatment discontinuation.

Manufacturing and marketing authorization holders in Japan must perform post-marketing surveys on new drugs to enable the Ministry of Health, Labour, and Welfare (MHLW) to re-examine the efficacy and safety of the therapeutic for a specified period after marketing approval. The present study is 1 of the 4 post-marketing surveys that comprise the mirabegron surveillance program.[10,18]

This study was conducted to evaluate the safety, efficacy, and persistence data that were acquired following the long-term use of mirabegron to treat patients with OAB symptoms in the real-world setting. The interim 1-year results from this study showed that OAB treatment with mirabegron was well tolerated and treatment effectiveness was maintained.[19] In addition, high mirabegron persistence was noted, which was greater in patients aged ≥65 years compared with those aged <65 years. This paper provides the final 3-year data from this study.

2 | METHODS

This study was conducted in accordance with the Good Post-marketing Study Practice (GPSP) standards of the MHLW.[20]

2.1 | Study design

The methodology used for this prospective investigation has been reported previously.[19] Briefly, patients were registered for the study during 2012 and 2013, and the study was conducted from October 2012 to September 2016. The study population comprised patients who received mirabegron for the treatment of urinary urgency, daytime frequency, and urgency urinary incontinence symptoms associated with OAB who had no previous mirabegron treatment history. The usual adult dose of mirabegron in Japan is 50 mg once daily after a meal.[21] The

initial dose should be reduced to 25 mg once daily in patients with moderate hepatic function (Child–Pugh score 7–9) or severe renal impairment (estimated glomerular filtration rate 15–29 mL/min/1.73 m^2). Internet-based patient registration and data collection were performed by the investigators using an electronic data capturing system.

2.2 | Study assessments

Patient characteristics were collected at the start of treatment. Mirabegron and concomitant medication (including OAB medication) use were analyzed during the study.

In terms of safety, ADRs (which included abnormal findings from laboratory or other tests) were collected during the entire study period. An annual classification system was used to examine the ADR results that were obtained every 3 months (apart from the first 3 months of the study, for which data were stratified into <1- and ≥1 to <3-month intervals). An ADR was defined as an adverse event (AE) that was considered by the investigators to be either potentially related to mirabegron treatment or had an unknown relationship with mirabegron treatment. Owing to the observational nature of the study, ADRs were analyzed rather than AEs, because the physicians may not have reported all the events that were unrelated to mirabegron treatment. Residual urine volume measurements were conducted at the start of treatment, after 3 and 6 months, and every 6 months thereafter (or at discontinuation).

For the efficacy analyses, Overactive Bladder Symptom Score (OABSS) was evaluated at the same time points as the residual urine volume assessments. Changes from baseline in OAB symptoms were investigated after 1, 2, and 3 years of treatment (or at discontinuation). Mirabegron treatment was subsequently judged to be "effective", "not effective", or "not assessable". A positive response to treatment (OAB disappearance) was defined as a reduction in the score for Question 3 on the OABSS to <2 points or total OABSS to <3 points. A minimal clinically important change (MCIC) was defined as an improvement in OABSS of ≥3 points from baseline. Changes in the number of patients with an MCIC over time were also assessed.

Treatment persistence rate was estimated using the Kaplan–Meier method. Using this technique, patients who stopped mirabegron treatment were defined as having a discontinuation event. Reasons for treatment discontinuation were collected and analyzed according to the time of the event. Conversely, patients who continued taking mirabegron during the study, were lost to follow-up, or did not complete the survey were censored at the final administration.

2.3 | Statistical analyses

The target registration cohort was 1000 patients to obtain a sample size of 300 patients who had an observation period of ≥1 year. The sample size was estimated to detect an ADR with a frequency of 1%, assuming a confidence level of 95%, in patients who received long-term mirabegron treatment. Approximately 30%–40% of the patients who started treatment were assumed to be receiving mirabegron after 52 weeks of therapy.

The safety analysis set consisted of patients without registration violations who received mirabegron and had ≥1 study visit after the initial receipt of medication. Patients diagnosed with OAB and who qualified for efficacy assessment according to the attending physicians

were included in the efficacy analysis set. The OABSS analysis set consisted of patients who did not have major diseases or conditions that excluded an OAB diagnosis (abnormal bladder, perivesical abnormalities, abnormalities of the prostate or urethra, urinary tract or genital infections, urinary retention, polyuria, or psychogenic pollakiuria)[22] were diagnosed with OAB using the OABSS, and were evaluated at baseline and at the final assessment using the OABSS with no missing data.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). For the residual urine volume and OABSS efficacy assessments, changes from baseline at each time point were evaluated using Wilcoxon's signed-rank test. Using the log-rank test, treatment discontinuation was assessed according to age (≤64, 65–74, and ≥75 years), sex, and therapy status (monotherapy vs. combination therapy, which was defined as treatment with ≥1 OAB agent other than mirabegron during the study period). Significance was set at 2-sided $P < 0.05$. Adjustments for Type I error based on multiple hypothesis testing were not performed in this study.

3 | RESULTS

3.1 | Study population

Data were collected from 1252 patients who were recruited from 177 medical institutions. Of these, 1138 patients were included in both the safety and efficacy analysis sets and 493 patients were included in the OABSS analysis set (Figure 1).

The mean ±SD age of the patient population was 71.9 ± 11.0 years, with an approximately equal number of men and women participating in the study (564 [49.6%] vs. 574 [50.4%] patients, respectively; Table 1). Similar proportions of patients were included in each of the OAB disease duration categories at baseline. Most patients had moderate disease (682 patients; 59.9%) and a wet disease classification (712 patients; 62.6%). Most patients (769 patients; 67.6%) had concurrent diseases, the most common being prostatic hyperplasia (355 patients; 31.2%), high blood pressure (173 patients; 15.2%), and hypertension (111 patients; 9.8%).

In all, 505 (44.4%), 339 (29.8%), and 242 (21.3%) patients received mirabegron treatment for ≥1, ≥2, and ≥3 years, respectively (Table 2). Most patients received a mean daily dose of mirabegron 50 mg (941 patients; 82.7%). Of the 66 (5.8%) patients receiving other OAB medications, 31 (2.7%) received solifenacin and 22 (1.9%) received imidafenacin (all other medications were received by <1.0% of patients).

3.2 | Safety

In all, 97 (8.52%) patients experienced 109 ADRs during the study (Table 3). The highest incidence of ADRs was reported <1 month (27 patients; 2.37%), ≥3 to <6 months (16 patients; 1.99%), and ≥1 to
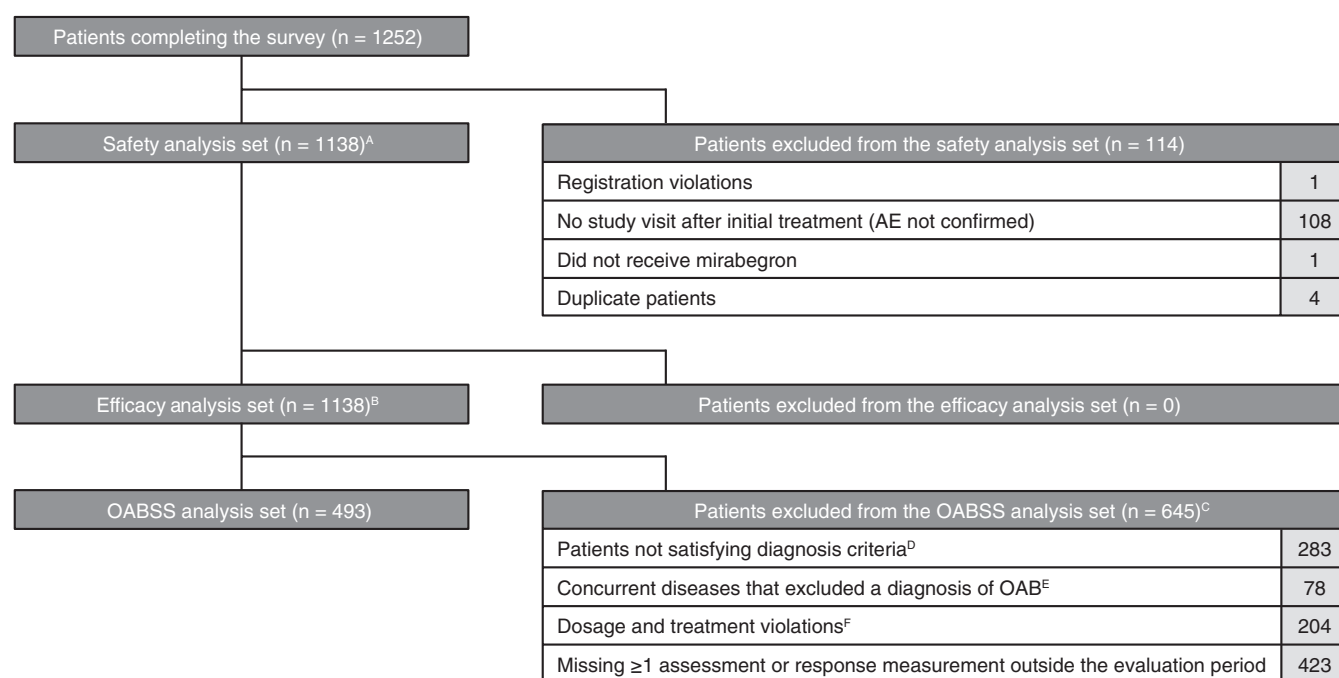

Patients completing the survey (n = 1252)	

Safety analysis set (n = 1138)[A]	Patients excluded from the safety analysis set (n = 114)	
	Registration violations	1
	No study visit after initial treatment (AE not confirmed)	108
	Did not receive mirabegron	1
	Duplicate patients	4

Efficacy analysis set (n = 1138)[B]	Patients excluded from the efficacy analysis set (n = 0)

OABSS analysis set (n = 493)	Patients excluded from the OABSS analysis set (n = 645)[C]	
	Patients not satisfying diagnosis criteria[D]	283
	Concurrent diseases that excluded a diagnosis of OAB[E]	78
	Dosage and treatment violations[F]	204
	Missing ≥1 assessment or response measurement outside the evaluation period	423

FIGURE 1 Patient disposition. [A] The safety analysis set consisted of patients without registration violations who received mirabegron and had ≥1 study visit after the initial receipt of medication. [B] The efficacy analysis set consisted of patients diagnosed with overactive bladder (OAB) and who qualified for efficacy assessment according to the attending physicians. [C] Including duplicated patients. [D] Patients whose Overactive Bladder Symptom Score (OABSS) for Question 3 was <2 points at baseline or whose total OABSS was <3 points at baseline. [E] Patients with abnormal bladder, including bladder cancer, bladder calculus, or interstitial cystitis (bladder pain syndrome), perivesical abnormalities (e.g. endometriosis), abnormalities of the prostate or urethra (prostate cancer or urethral calculus), urinary tract or genital infections (bacterial cystitis, prostatitis, or urethritis), or other conditions (urinary retention, polyuria, or psychogenic pollakiuria).[22] [F] Patients who were not treated using a daily dose of mirabegron 50 mg and not treated once daily. However, patients with moderate hepatic impairment, as determined by the Child–Pugh score and/or classification criteria for the severity of adverse drug reactions (ADRs), or patients with severe renal impairment, as determined by the classification criteria for severity of ADRs (estimated glomerular filtration rates were not known in the present study) who were not treated at an initial daily dose of mirabegron 25 mg were regarded as having a dosage deviation and were excluded from the analysis set

TABLE 1 Patient demographics and baseline characteristics (n = 1138)

Sex	
Male	564 (49.6)
Female	574 (50.4)
Age (y)	71.9 ± 11.0
Age groups	
≤64 y	231 (20.3)
65–74 y	384 (33.7)
≥75 y	523 (46.0)
BMI (kg/m^2)	23.45 ± 4.04
Duration of OAB disease	
<3 mo	226 (19.9)
≥3 mo−<1 y	236 (20.7)
≥1−<3 y	303 (26.6)
≥3 y	265 (23.3)
Unknown	108 (9.5)
OAB severity[A]	
Mild	166 (14.6)
Moderate	682 (59.9)
Severe	137 (12.0)
Unknown	153 (13.4)
OAB disease classification[B]	
Dry	275 (24.2)
Wet	712 (62.6)
Unknown	151 (13.3)
Residual urine volume (mL)	19.531 ± 31.320
Concurrent diseases[C]	
Yes	769 (67.6)
No	328 (28.8)
Unknown	41 (3.6)
Major concurrent diseases in ≥2.0% of patients[C]	
Prostatic hyperplasia	355 (31.2)
High blood pressure	173 (15.2)
Hypertension	111 (9.8)
Hyperlipidemia	94 (8.3)
Diabetes mellitus	78 (6.9)
Insomnia	47 (4.1)
Prostate cancer	43 (3.8)
Osteoporosis	37 (3.3)
Neurogenic bladder	31 (2.7)
Constipation	28 (2.5)
Reflux esophagitis	26 (2.3)
Hypercholesterolemia	25 (2.2)
Hyperuricemia	23 (2.0)

Data are shown for the safety analysis set and are given as n (%) or as mean ± SD.

[A] The severity of overactive bladder (OAB) was based on the total Overactive Bladder Symptom Score (OABSS) at baseline (mild: 0–5; moderate: 6–11; severe: 12–15).

[B] Dry disease was defined as 0 points for Question 4 on the OABSS; wet disease was defined as ≥1 point for Question 4 on the OABSS.

[C] Concurrent diseases are shown as reported verbatim by the attending physician.

BMI, body mass index; SD, standard deviation.

<3 months (18 patients; 1.79%) after starting treatment. Using the annual classification system, the incidence of ADRs decreased over time (<1 year: 1.34%–2.37%; ≥1 and <2 years: 0.45%–1.60%;

and ≥2 and <3 years: 0.29%–1.10%). No cumulative events and no delayed specific ADRs were observed during the study.

The most common ADRs reported were constipation (19 patients; 1.67%), residual urine volume increased (14 patients; 1.23%), and dysuria (10 patients; 0.88%). Of the 109 ADRs reported, 7 serious ADRs were reported by 7 patients, all of whom were aged ≥65 years, namely rectal cancer, prostatitis, osteoporosis, breast cancer (female), urinary retention, gallbladder cancer, and anti-neutrophil cytoplasmic antibody-positive vasculitis. Only urinary retention was considered to be possibly related to mirabegron treatment; an unknown relationship was reported for the others.

At baseline, mean ±SD residual urine volume was 19.531 ± 31.320 mL. In general, no significant changes in residual urine volume were observed during the course of the study (Figure 2). The only exceptions were the 2.5- and 3-year time points, at which residual urine volume had decreased significantly from baseline by a mean ±SD of −6.605 ± 30.836 mL (P = 0.034) and −4.656 ± 27.041 mL (P = 0.026), respectively.

3.3 | Efficacy

Mirabegron was considered to be an effective treatment for 842 of 1082 (77.8%) patients at the final assessment using an efficacy rating judged by the investigators. In all, 279 of the 493 (56.6%) patients included in the OABSS analysis set achieved OAB disappearance. At the final assessment, 321 (65.1%) patients achieved an MCIC.

At baseline, mean ±SD OABSS was 9.0 ± 2.36 points. At all time points evaluated throughout the study, there were significant decreases in OABSS compared with baseline (P < 0.001) and all the mean decreases observed were larger than the MCIC (Figure 3). At the time of the final assessment, mean ±SD decrease in OABSS was −4.1 ± 3.4.

Of the 133 patients who achieved an MCIC within ≤1 year, 117 (88.0%) also satisfied the criteria for an MCIC between 1 and ≤2 years (Figure 4). Of these, 80 of 89 (89.9%) patients subsequently satisfied the criteria for an MCIC after >2 years.

3.4 | Persistence

According to the Kaplan–Meier method, overall treatment persistence rates were 65.8%, 52.9%, and 46.7% after 1, 2, and 3 years of mirabegron treatment, respectively (Figure 5a). During the observation period, 896 (78.7%) patients discontinued or dropped out from the study (Table 4). As shown by the decreasing yearly discontinuation or dropout rate (<1 year: 633/1138 [55.6%] patients; ≥1 and <2 years: 166/505 [32.9%] patients; and ≥2 and <3 years: 97/339 [28.6%] patients), patients who completed 1 year of mirabegron treatment generally persisted with the medication throughout the rest of the study. Most patients who discontinued did so because of either incomplete visits during the survey (434 patients; 48.4%) or discontinuation or dropout during the observation period (443 patients; 49.4%). The most common reasons for discontinuing the study for the patients who discontinued or dropped out were unchanged or aggravated symptoms (158 patients; 17.6%), symptom remission (118 patients; 13.2%), and patient's request (116 patients; 12.9%). The proportion of patients who discontinued from the study due to the onset of AEs did not increase over time following the long-term use of

TABLE 2 Mirabegron treatment status (n = 1138)

Patients receiving treatment	
≥1 mo	1003 (88.1)
≥3 mo	804 (70.7)
≥6 mo	672 (59.1)
≥1 y	505 (44.4)
≥1.5 y	411 (36.1)
≥2 y	339 (29.8)
≥2.5 y	272 (23.9)
≥3 y	242 (21.3)
Daily mirabegron dose at start	
25 mg	175 (15.4)
>25—<50 mg	0
50 mg	963 (84.6)
Maximum daily mirabegron dose	
25 mg	124 (10.9)
>25—<50 mg	0
50 mg	1014 (89.1)
Mean daily mirabegron dose	
25 mg	124 (10.9)
>25—<50 mg	73 (6.4)
50 mg	941 (82.7)
OAB medication other than mirabegron	
No	1023 (89.9)
Yes	66 (5.8)
Solifenacin succinate	31 (2.7)
Imidafenacin	22 (1.9)
Fesoterodine fumarate	9 (0.8)
Propiverine hydrochloride	8 (0.7)
Oxybutynin hydrochloride (for external use)	5 (0.4)
Tolterodine tartrate	3 (0.3)
Unknown	49 (4.3)

Data are shown for the safety analysis set and are given as n (%).

mirabegron (<1 year: 48 [7.6%] patients; ≥1 and <2 years: 10 [6.0%] patients; and ≥2 and <3 years: 7 [7.2%] patients).

Results were then stratified according to age. In the ≤64 years age group, 1-, 2-, and 3-year persistence rates were 59.8%, 48.6%, and 46.3%, respectively; in those aged 65–74 years, the corresponding rates were 67.5%, 56.0%, and 48.4%, whereas for those aged ≥75 years the rates were 66.7%, 52.3%, and 45.9%, respectively (Figure 5b). Patients who were ≤64 years of age were more likely to discontinue treatment during the earlier phases of the study compared with the other 2 age groups. However, no significant differences were noted among the age groups in the overall persistence rates (log-rank test, P = 0.297). In all, 195 of 231 (84.4%), 294 of 384 (76.6%), and 407 of 523 (77.8%) patients in the ≤64, 65–74, and ≥75 year age groups discontinued or dropped out from the study (Table 5). In all age groups, the most common reason for discontinuing the study for the patients who discontinued or dropped out was unchanged or aggravated symptoms (29 [14.9%], 54 [18.4%] and 75 [18.4%] patients for those aged ≤64, 65–74, and ≥75 years, respectively). However, the proportion of patients who discontinued from the study due to the onset of AEs was higher in the ≥75 years

TABLE 3 Adverse drug reactions (ADR) by time of onset

	Time from start of mirabegron treatment to ADR onset															Cumulative total
	<1 mo	≥1–<3 mo	≥3–<6 mo	≥6–<9 mo	≥9 mo–<1 year	≥1–<1.25 y	≥1.25–<1.5 y	≥1.5–<1.75 y	≥1.75–<2 y	≥2–<2.25 y	≥2.25–<2.5 y	≥2.5–<2.75 y	≥2.75–<3 y	≥3 y	Unknown	
No. patients	1138	1003	804	672	575	505	443	411	376	339	291	272	258	242	–	1138
No. patients with ADRs	27	18	16	9	9	6	2	3	6	1	2	3	2	0	3	97
No. ADRs	30	19	17	10	9	6	3	3	6	1	2	3	2	0	3	109
% Patients with ADRs	2.37	1.79	1.99	1.34	1.57	1.19	0.45	0.73	1.60	0.29	0.69	1.10	0.78	0.00	–	8.52
ADR by preferred term reported by ≥0.20% of all patients																
Constipation	7 (0.62)	5 (0.50)	4 (0.50)	1 (0.15)	1 (0.17)	1 (0.20)	0	0	1 (0.27)	0	0	0	0	0	0	19 (1.67)
Residual urine volume increased	4 (0.35)	1 (0.10)	3 (0.37)	1 (0.15)	1 (0.17)	0	0	0	0	0	1 (0.34)	2 (0.74)	1 (0.39)	0	0	14 (1.23)
Dysuria	6 (0.53)	1 (0.10)	1 (0.12)	0	0	1 (0.20)	0	0	0	0	0	1 (0.37)	0	0	0	10 (0.88)
Cystitis	0	2 (0.20)	4 (0.50)	2 (0.30)	2 (0.35)	2 (0.40)	0	0	1 (0.27)	0	0	0	0	0	0	9 (0.79)
Thirst	1 (0.09)	0	2 (0.25)	0	0	0	0	1 (0.24)	0	0	0	0	0	0	2	6 (0.53)
Urinary retention	0	1 (0.10)	0	3 (0.45)	0	1 (0.20)	0	0	1 (0.27)	0	0	0	0	0	0	6 (0.53)
Abdominal discomfort	1 (0.09)[A]	2 (0.20)	0	0	0	0	0	0	0	0	0	0	0	0	0	3 (0.26)
Nausea	2 (0.18)	1 (0.10)	0	0	0	0	0	0	0	0	0	0	0	0	0	3 (0.26)

Data are shown for the safety analysis set and, unless indicated otherwise, are given as n (%).
[A] The ADR was reported by the investigator as a "gastrointestinal symptom" with specific symptoms unknown.
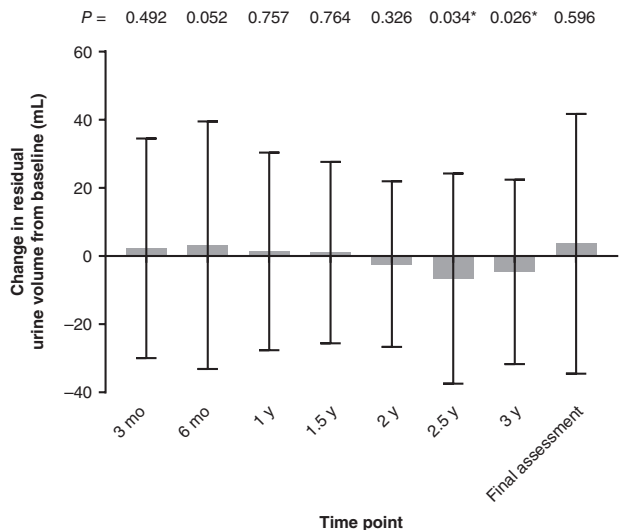
$P =$ 0.492   0.052   0.757   0.764   0.326   0.034*   0.026*   0.596

FIGURE 2 Mean ±SD changes in residual urine volume from baseline. Data are shown for the safety analysis set. *$P < 0.05$ compared with baseline. SD, standard deviation
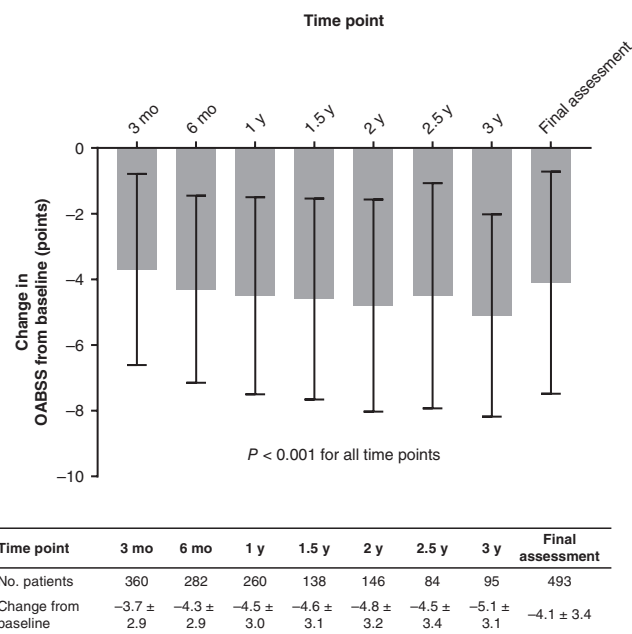
Time point	3 mo	6 mo	1 y	1.5 y	2 y	2.5 y	3 y	Final assessment
No. patients	335	237	208	123	132	75	82	474
Change from baseline (mL)	2.268 ± 32.209	3.185 ± 36.323	1.350 ± 28.983	0.999 ± 26.637	−2.371 ± 24.320	−6.605 ± 30.836	−4.656 ± 27.041	3.590 ± 38.121

FIGURE 3 Changes from baseline in Overactive Bladder Symptom Score (OABSS). Data are shown for the OABSS analysis set (patients who did not have major diseases or conditions that excluded an overactive bladder [OAB] diagnosis [abnormal bladder, including bladder cancer, bladder calculus, or interstitial cystitis {bladder pain syndrome}], perivesical abnormalities [e.g. endometriosis], abnormalities of the prostate or urethra [prostate cancer or urethral calculus], urinary tract or genital infections [bacterial cystitis, prostatitis, or urethritis], or other conditions [urinary retention, polyuria, or psychogenic pollakiuria]),[22] who were diagnosed with OAB using the OABSS and were evaluated at baseline and at the final assessment using the OABSS, with no missing data. Results are given as mean ± SD. SD, standard deviation

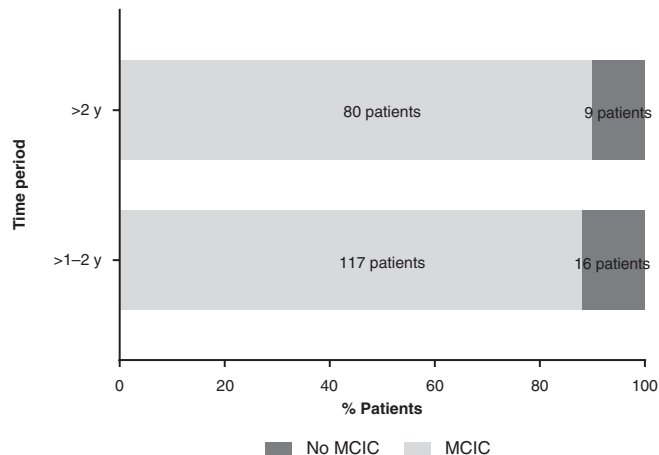| Time point	3 mo	6 mo	1 y	1.5 y	2 y	2.5 y	3 y	Final assessment
No. patients	360	282	260	138	146	84	95	493
Change from baseline	−3.7 ± 2.9	−4.3 ± 2.9	−4.5 ± 3.0	−4.6 ± 3.1	−4.8 ± 3.2	−4.5 ± 3.4	−5.1 ± 3.1	−4.1 ± 3.4

FIGURE 4 Proportion of patients who satisfied the criteria for a minimal clinically important change (MCIC) of the patients who achieved an MCIC in the previous year. Data are shown for the Overactive Bladder Symptom Score (OABSS) analysis set (patients who did not have major diseases or conditions that excluded an overactive bladder [OAB] diagnosis [abnormal bladder, including bladder cancer, bladder calculus, or interstitial cystitis {bladder pain syndrome}], perivesical abnormalities [e.g. endometriosis], abnormalities of the prostate or urethra [prostate cancer or urethral calculus], urinary tract or genital infections [bacterial cystitis, prostatitis, or urethritis], or other conditions [urinary retention, polyuria, or psychogenic pollakiuria]),[22] who were diagnosed with OAB using the OABSS and were evaluated at baseline and at the final assessment using the OABSS, with no missing data

age group (41 patients; 10.1%) than in the ≤64 and 65–74 years age groups (7 [3.6%] and 17 [5.8%] patients, respectively).

Similar persistence rates at 1, 2, and 3 years were observed in men (65.9%, 51.3%, and 43.4%, respectively) and women (65.7%, 54.9%, and 51.1%, respectively; log-rank test, $P = 0.365$; see Figure S1a, available as Supplementary Material to this paper). In total, 435 of 564 (77.1%) men and 461 of 574 (80.3%) women discontinued or dropped out from the study (Table S1). For both sexes, the most common reason for discontinuing the study for the patients who discontinued or dropped out was unchanged or aggravated symptoms. However, a higher incidence was observed in men than women (96 [22.1%] vs. 62 [13.4%] patients, respectively).

Patients who received combination therapy had significantly higher persistence rates at 1, 2, and 3 years (84.8%, 76.9%, and 58.4%, respectively) than those who received monotherapy (64.6%, 50.9%, and 46.2%, respectively; log-rank test, $P = 0.007$; Figure S1b). Overall, 815 of 1023 (79.7%) patients receiving monotherapy and 42 of 66 (63.6%) receiving combination therapy discontinued or dropped out from the study (Table S2). Similar to the overall safety analysis set, the most common reason for discontinuing the study for the patients who discontinued or dropped out was unchanged or aggravated symptoms in the monotherapy group (141 patients; 17.3%), whereas in the combination therapy group, which had a smaller number of patients, the most common reason for discontinuing the study was the onset of AEs (6 patients; 14.3%).

4 | DISCUSSION

The present study is the first to examine the safety, efficacy, and persistence of mirabegron therapy over a 3-year period in the real-world
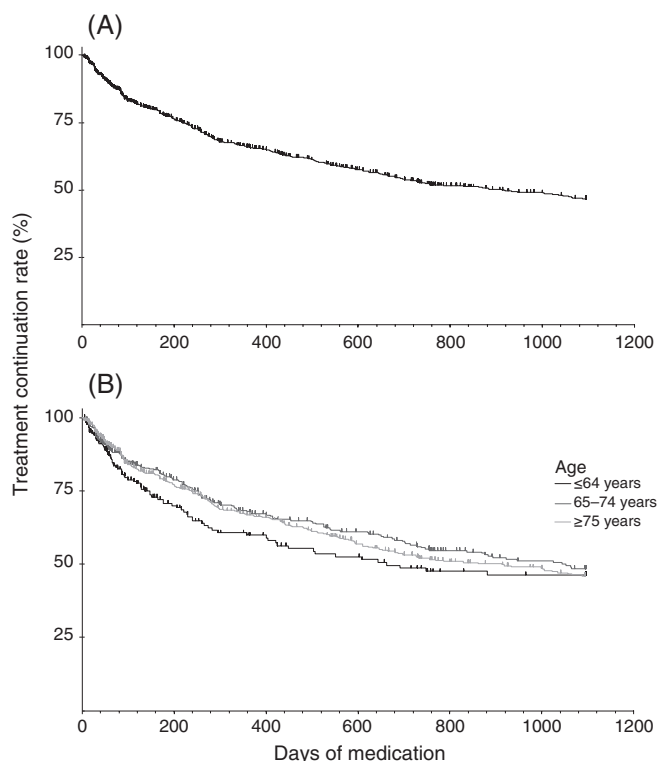
FIGURE 5 Kaplan–Meier curves showing patient persistence; A, overall data; B, stratified according to age

setting. Importantly, the safety results obtained in this study indicate that the incidence of ADRs decreases with ongoing mirabegron treatment, and therefore mirabegron is well tolerated in the long term. The efficacy results demonstrated that most patients who responded positively to mirabegron treatment in the first year continued to respond over the 3-year study. In addition, according to the Kaplan–Meier method, approximately half the patients were still persisting with mirabegron treatment by the end of the study.

The safety findings from this study showed that mirabegron was well tolerated. Similar safety profiles were observed for mirabegron in

previous studies that evaluated the safety of 1 year of mirabegron treatment.[11,23] Interestingly, an annual classification system showed that the incidence of ADRs actually decreased year on year during the present study. In support of this finding, no cumulative events and no delayed specific ADRs were observed during the study. The most common ADRs in this study were constipation, residual urine volume increased, and dysuria. This finding is supported by previous real-world Japanese studies that have investigated the safety and efficacy of mirabegron.[10,24] In general, no significant increases in residual urine volume were noted in this study. However, because increases in residual urine volume are associated with urinary tract infections,[25] physicians must continue to monitor patients on a regular basis.

Mirabegron was considered to be an effective treatment for most patients over the 3-year study period. More than half the patients achieved an MCIC and experienced OAB disappearance. Similar efficacy findings were observed in a 12-week post-marketing survey that has also been conducted as part of the mirabegron surveillance program.[10] In the present study, significant improvements in OABSS were noted from the first time point evaluated and were maintained throughout the rest of the 3-year study period. Similar OABSS results have also been observed in a 2-year post-marketing solifenacin study.[26] In addition, the OABSS findings from the present study are supported by the efficacy results from previous 1-year Phase III mirabegron trials, which also noted significant improvements in efficacy from the first time point onwards.[11,23] We believe that the present study is the first to demonstrate that approximately 90% of patients who achieved an MCIC following 1 year of mirabegron therapy continued to satisfy the criteria for an MCIC after a further year of treatment. These data suggest that mirabegron treatment may not desensitize or downregulate β3-adrenoreceptors, a result that supports some of the findings from previous in vitro investigations.[27,28]

High treatment persistence results were noted with mirabegron throughout the present 3-year study. A persistence rate of 65.8% was observed after 1 year of treatment with mirabegron, which is higher than the 1-year rates of 12.2%–53.5% that have been typically reported in previous mirabegron studies.[14,16,17,29–34] The higher rates

TABLE 4 Discontinuation or dropping out from the study according to time period

		Time period		
	Patients in the SAF	**<1 y**	**≥1–<2 y**	**≥2–<3 y**
No. patients	1138	1138	505	339
Patients who did not discontinue or drop out	242 (21.3)	505 (44.4)	339 (67.1)	242 (71.4)
Patients who discontinued or dropped out	896 (78.7)	633 (55.6)	166 (32.9)	97 (28.6)
Reason for discontinuation[A]				
Incomplete visits	434 (48.4)	314 (49.6)	67 (40.4)	53 (54.6)
Discontinued or dropped out[B]	443 (49.4)	319 (50.4)	89 (53.6)	35 (36.1)
Onset of adverse events	65 (7.3)	48 (7.6)	10 (6.0)	7 (7.2)
Unchanged or aggravated symptoms	158 (17.6)	117 (18.5)	29 (17.5)	12 (12.4)
Symptom remission	118 (13.2)	77 (12.2)	35 (21.1)	6 (6.2)
Patient's request	116 (12.9)	89 (14.1)	18 (10.8)	9 (9.3)
Other reasons	19 (2.1)	12 (1.9)	4 (2.4)	3 (3.1)
Other	19 (2.1)	0	10 (6.0)	9 (9.3)

Data are shown for the safety analysis set (SAF) and, unless indicated otherwise, are given as n (%).
[A] Percentages are for the number of patients who dropped out.
[B] Patients may have had more than 1 reason for discontinuing or dropping out.

TABLE 5 Discontinuation or dropping out from the study according to time period and age group

		Time period		
	Patients in the SAF	<1 y	≥1–<2 y	≥2–<3 y
Age ≤64 y				
No. patients	231	231	70	48
Patients who did not discontinue or drop out	36 (15.6)	70 (30.3)	48 (68.6)	36 (75.0)
Patients who discontinued or dropped out	195 (84.4)	161 (69.7)	22 (31.4)	12 (25.0)
Reason for discontinuation[A]				
Incomplete visits	110 (56.4)	94 (58.4)	8 (36.4)	8 (66.7)
Discontinued or dropped out[B]	81 (41.5)	67 (41.6)	12 (54.5)	2 (16.7)
Onset of adverse events	7 (3.6)	5 (3.1)	2 (9.1)	0
Unchanged or aggravated symptoms	29 (14.9)	25 (15.5)	4 (18.2)	0
Symptom remission	24 (12.3)	20 (12.4)	4 (18.2)	0
Patient's request	21 (10.8)	17 (10.6)	2 (9.1)	2 (16.7)
Other reasons	2 (1.0)	2 (1.2)	0	0
Other	4 (2.1)	0	2 (9.1)	2 (16.7)
Age 65–74 y				
No. patients	384	384	182	130
Patients who did not discontinue or drop out	90 (23.4)	182 (47.4)	130 (71.4)	90 (69.2)
Patients who discontinued or dropped out	294 (76.6)	202 (52.6)	52 (28.6)	40 (30.8)
Reason for discontinuation[A]				
Incomplete visits	140 (47.6)	99 (49.0)	20 (38.5)	21 (52.5)
Discontinued or dropped out[B]	147 (50.0)	103 (51.0)	28 (53.8)	16 (40.0)
Onset of adverse events	17 (5.8)	12 (5.9)	2 (3.8)	3 (7.5)
Unchanged or aggravated symptoms	54 (18.4)	38 (18.8)	10 (19.2)	6 (15.0)
Symptom remission	38 (12.9)	23 (11.4)	12 (23.1)	3 (7.5)
Patient's request	43 (14.6)	35 (17.3)	5 (9.6)	3 (7.5)
Other reasons	7 (2.4)	5 (2.5)	0	2 (5.0)
Other	7 (2.4)	0	4 (7.7)	3 (7.5)
Age ≥75 y				
No. patients	523	523	253	161
Patients who did not discontinue or drop out	116 (22.2)	253 (48.4)	161 (63.6)	116 (72.0)
Patients who discontinued or dropped out	407 (77.8)	270 (51.6)	92 (36.4)	45 (28.0)
Reason for discontinuation[A]				
Incomplete visits	184 (45.2)	121 (44.8)	39 (42.4)	24 (53.3)
Discontinued or dropped out[B]	215 (52.8)	149 (55.2)	49 (53.3)	17 (37.8)
Onset of adverse events	41 (10.1)	31 (11.5)	6 (6.5)	4 (8.9)
Unchanged or aggravated symptoms	75 (18.4)	54 (20.0)	15 (16.3)	6 (13.3)
Symptom remission	56 (13.8)	34 (12.6)	19 (20.7)	3 (6.7)
Patient's request	52 (12.8)	37 (13.7)	11 (12.0)	4 (8.9)
Other reasons	10 (2.5)	5 (1.9)	4 (4.3)	1 (2.2)
Other	8 (2.0)	0	4 (4.3)	4 (8.9)

Data are shown for the safety analysis set (SAF) and, unless indicated otherwise, are given as n (%).
[A] Percentages are for the number of patients who dropped out.
[B] Patients may have had more than 1 reason for discontinuing or dropping out.

in the present study may be due to differences between Japan and other countries in terms of healthcare systems, although some of the 1-year studies were conducted in Japan.[17,30–32] Alternatively, the differences may reflect the prospective study design used herein, which may have favorably affected patient attitudes and involved frequent clinical consultations. However, a minority of the 1-year studies also involved a prospective study design.[29,31] In agreement with the findings of the present study, high 1-year persistence rates of 63% and 70.9% were observed in a retrospective

Japanese study[35] and a prospective Czech study.[36] In addition, 2- and 3-year persistence rates of 56% and 52%, respectively, were reported in the Japanese investigation,[35] a finding that corresponds with the results of the present study (52.9% and 46.7% at 2 and 3 years, respectively). Our investigation also showed that out of the patients who persisted with mirabegron therapy over the first year of treatment, most persisted with treatment over the rest of the study. This may reflect the high MCIC rate over time and the low rate of ADRs in this study.

It is vitally important to explore why patients with OAB tend to discontinue medication because good adherence to drug therapy is known to be associated with positive health outcomes.[37] The most common reason for discontinuing from the present study was unchanged or aggravated symptoms. Although direct comparisons are inappropriate, this finding is broadly consistent with previous mirabegron studies that have evaluated persistence in the UK and Japan.[29–32]

A treatment persistence rate of 46.7% was noted after 3 years of mirabegron treatment according to the Kaplan–Meier method. In contrast, 896 (78.7%) patients discontinued or dropped out from the study. The difference between the 2 results stems from the methodologies used to calculate the results. Using the Kaplan–Meier method, only patients who stopped mirabegron treatment were defined as having a discontinuation event. Patients who were lost to follow-up or did not complete the survey were censored at the final administration.

Overall, the age and sex of the patients did not significantly affect the persistence results achieved over the study period. In support of the age findings from this investigation, a prospective multicenter study found that age did not have a significant effect on study discontinuation.[36] However, the present study showed that patients who were aged ≤64 years were more likely to discontinue treatment during the initial stages of the study compared with those in the other 2 age groups. This finding is in agreement with the results of several 1-year persistence studies, which found that older patients persisted with mirabegron treatment for a longer period of time than younger individuals.[16,17,33] Mixed results have been reported in previous 1-year persistence studies that have examined the effect of sex on discontinuation of mirabegron treatment. Two studies conducted in Canada and the Czech Republic showed that mirabegron persistence rates were higher in women than in men,[16,36] whereas the reverse was found in 2 Japanese- and UK-based studies.[17,33]

The strengths of the present study are due to its wide-ranging nature. Post-marketing surveillance data can provide useful information and an opportunity to identify ADRs that did not occur during pre-marketing clinical trials. Unlike clinical trials, post-marketing studies can generate data from a representative sample of the population within a wide variety of real-world clinical settings. In addition, the heterogeneous population of patients observed in a post-marketing surveillance study is more representative of the real-world situation and can therefore provide a greater opportunity to detect specific risks associated with therapy. However, the present study does have some limitations that are primarily related to the observational nature of the investigation. In post-marketing studies, the onset of ADRs may be affected by various patient characteristics and concomitant medications, thereby making it difficult to determine their causal relationship with the study drug. Furthermore, this study only involved a single cohort of patients. No control or comparator group was used in the study and there was no randomization according to age or treatment group.

In conclusion, the present study demonstrated the safety, efficacy, and persistence of 3-year treatment with mirabegron in patients with OAB symptoms in the real-world clinical setting. Mirabegron treatment was well tolerated over the duration of the study; reported ADRs were generally consistent with the known safety profile of mirabegron and no new safety risks were identified from this surveillance. Mirabegron was an effective treatment with early improvements in OABSS that were maintained over the 3-year treatment period. High persistence with mirabegron treatment was observed; approximately two-thirds of patients were persisting with treatment after 1 year and almost half were still receiving mirabegron after 3 years.

CONFLICTS OF INTEREST

All authors are employees of Astellas Pharma Inc.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.