Safety, efficacy and persistence following daily mirabegron use for overactive bladder: 3-year results from a Japanese post-marketing surveillance study

Kato D[1], Tabuchi H[1], Uno S[2]

[1]Medical Science, Medical Affairs, Astellas Pharma Inc., Tokyo, Japan and [2]Japan-Asia Data Science, Development, Astellas Pharma Inc., Tokyo, Japan

INTRODUCTION

- Antimuscarinics are commonly used for treating patients with overactive bladder (OAB) symptoms, despite being associated with anticholinergic side effects.[1] The β3-adrenoreceptor agonist, mirabegron, has a different mechanism of action,[2,3] which may circumvent these adverse effects
- The efficacy and safety of mirabegron over a 1-year treatment period have been demonstrated in a previous Phase III Japanese study involving patients with OAB symptoms.[4] However, efficacy and safety data from the real-world setting are currently lacking
- Increased treatment persistence can also be achieved with mirabegron compared with antimuscarinics.[5–7] These studies only lasted 1 year and did not investigate reasons for treatment discontinuation

OBJECTIVES

- To evaluate the safety, efficacy, and persistence data that were acquired over 3 years following the use of mirabegron to treat patients with OAB symptoms in the real-world setting

METHODS

Study design

- This study was a Japanese post-marketing surveillance investigation (ClinicalTrials.gov: NCT01901120)
  - The methodology used has been previously reported[8,9]
  - This investigation was conducted in accordance with the Good Post-marketing Study Practice (GPSP) standards of the Ministry of Health, Labour and Welfare (MHLW) in Japan[10]
- Patients were registered during 2012 and 2013, and the study was conducted from October 2012 to September 2016

Patients

- The study population was comprised of both men and women
- Patients were included 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
- Full patient histories were collected at the start of treatment. Mirabegron use was analyzed throughout the study

Safety assessments

- Adverse drug reactions (ADRs) were collected during the entire study period
- An annual classification system was used to examine the ADR results
  - For the first 3 months, the study data were stratified into <1-month and ≥1–<3-month intervals
  - Data were stratified every 3 months thereafter
- ADRs were defined as adverse events considered by the investigators to be potentially related to or to have an unknown relationship with mirabegron treatment
- Residual urine volume measurements were conducted at the start of treatment, after 3 and 6 months, and every 6 months until the end of the study or at treatment discontinuation

Efficacy assessments

- Overactive Bladder Symptom Score (OABSS) was evaluated at the start of treatment, after 3 and 6 months, and every 6 months until the end of the study or at treatment discontinuation
- Changes from Baseline in OAB symptoms were investigated after 1, 2, and 3 years of treatment or at treatment discontinuation
  - Mirabegron treatment was judged by the investigators to be "effective", "not effective", or "not assessable"
- A positive response to treatment (OAB disappearance) was defined as a reduction in OABSS question 3 to <2 points (sudden desire to urinate of less than once per week) or total OABSS to <3 points
- Changes in the number of patients with a minimal clinically important change (MCIC) in OABSS over time were also assessed
  - MCIC was defined as an improvement in OABSS of ≥3 points compared with Baseline

Persistence evaluations

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

Statistical analysis

- Analysis sets
  - Safety Analysis Set: patients without registration violations who received mirabegron and had ≥1 post-medication study visit
  - Efficacy Analysis Set (subset of the Safety Analysis Set): patients diagnosed with OAB who qualified for assessment according to the attending physicians
  - OABSS Analysis Set (subset of the Efficacy Analysis Set): patients without major diseases/conditions that excluded an OAB diagnosis, who were diagnosed with OAB using the OABSS, and who were evaluated at Baseline and at the final assessment using the OABSS with no missing data
- For the residual urine volume and OABSS assessments, changes from Baseline were evaluated using Wilcoxon signed rank test

RESULTS

Study population

- Data were collected from 1252 patients
  - 1138 patients were included in both the Safety and Efficacy Analysis Sets
  - 493 patients were included in the OABSS Analysis Set
- Mean age was 71.9 ± 10.95 years and 574 (50.4%) patients were women (Table 1)
- Mirabegron treatment
  - 505 (44.4%) patients received mirabegron for ≥1 year
  - 339 (29.8%) patients received mirabegron for ≥2 years
  - 242 (21.3%) patients received mirabegron for ≥3 years
- Most patients received a mean daily dose of mirabegron 50 mg (941 [82.7%] patients)

Safety

- Overall, 97 (8.52%) patients experienced 109 ADRs (Table 2)
- Using the annual classification system, the incidence of ADRs decreased over time
  - <1 year: 1.34% to 2.37%
  - ≥1 and <2 years: 0.45% to 1.60%
  - ≥2 and <3 years: 0.29% to 1.10%
- No cumulative events and no delayed specific ADRs were observed
- Most common ADRs
  - Constipation: 19 (1.67%) patients
  - Residual urine volume increased: 14 (1.23%) patients
  - Dysuria: 10 (0.88%) patients
- No significant increases in residual urine volume were observed

Efficacy

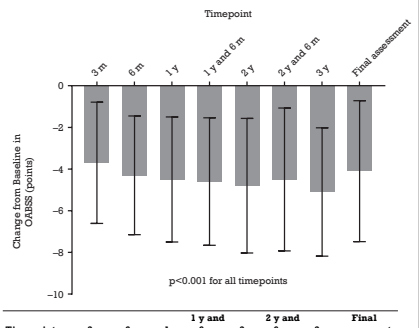
- Mirabegron was considered to be effective for 842/1082 (77.8%) patients at the final assessment
- Of the 493 patients in the OABSS Analysis Set
  - 279 (56.6%) achieved OAB disappearance
  - 321 (65.1%) achieved an MCIC
- Significant decreases in OABSS were reported for all timepoints (p<0.001) (Figure 1)
  - A mean decrease of −4.1 ± 3.38 in OABSS was noted at the final assessment
- Those patients who achieved an MCIC within ≤1 year typically continued to maintain an MCIC throughout the rest of the study
  - >1–≤2 years: 117/133 (88.0%) patients
  - >2 years: 80/89 (89.9%) patients

Table 1. Patient demographics and Baseline characteristics (Safety Analysis Set)

Variable	Patients (n=1138)
Sex, n (%)	
Male	564 (49.6)
Female	574 (50.4)
Age in y, mean ± SD	71.9 ± 10.95
Age group, n (%)	
≤64 y	231 (20.3)
65–74 y	384 (33.7)
≥75 y	523 (46.0)
BMI in kg/m², mean ± SD	23.45 ± 4.035
OAB disease duration, n (%)	
<3 m	226 (19.9)
≥3 m–<1 y	236 (20.7)
≥1–<3 y	303 (26.6)
≥3 y	265 (23.3)
Unknown	108 (9.5)
OAB severity, n (%)*	
Mild	166 (14.6)
Moderate	682 (59.9)
Severe	137 (12.0)
Unknown	153 (13.4)
OAB disease classification, n (%)†	
Dry	275 (24.2)
Wet	712 (62.6)
Unknown	151 (13.3)
Residual urine volume in mL, mean ± SD	19.531 ± 31.3200
Concurrent diseases, n (%)‡	
Yes	769 (67.6)
No	328 (28.8)
Unknown	41 (3.6)
Major concurrent diseases (≥2.0% of patients), n (%)‡	
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)

Adapted from Kato et al.[4] *Severity of total OABSS at Baseline (mild: 0–5, moderate: 6–11, severe: 12–15). †Dry disease: OABSS question 4 was 0 points (no urinary leakage), wet disease: OABSS question 4 was ≥1 point (urinary leakage that occurred at least less than once a week). ‡Concurrent diseases are shown as reported verbatim by the attending physician.
BMI=body mass index; OAB=overactive bladder; OABSS=Overactive Bladder Symptom Score; SD=standard deviation

Figure 1. Changes from Baseline in OABSS (OABSS Analysis Set)



Timepoint	3 m	6 m	1 y	1 y and 6 m	2 y	2 y and 6 m	3 y	Final assessment
Patients, n	360	282	260	138	146	84	95	493
Change from baseline, mean ± SD	−3.7 ± 2.91	−4.3 ± 2.85	−4.5 ± 3.00	−4.6 ± 3.06	−4.8 ± 3.23	−4.5 ± 3.43	−5.1 ± 3.08	−4.1 ± 3.38

Adapted from Kato et al.[4]
OABSS=Overactive Bladder Symptom Score; SD=standard deviation

Persistence

- Mirabegron treatment persistence rates using the Kaplan–Meier method (Figure 2)
  - 65.8% after 1 year of treatment
  - 52.9% after 2 years of treatment
  - 46.7% after 3 years of treatment
- During the 3-year observation period, 896 (78.7%) patients discontinued or dropped out from the study (Table 3)
- The most common reasons for discontinuation were incomplete visits during the survey (434 [48.4%] patients) and discontinuation/dropout during the observation period (443 [49.4%] patients; see Table 3 for specific reasons)

Table 3. Status of discontinuation/dropout according to time period (Safety Analysis Set)

Variable	Patients in the Safety Analysis Set	Time period		
		<1 y	≥1–<2 y	≥2–<3 y
Patients, n	1138	1138	505	339
Patients who did not discontinue/dropout, n (% of patients)	242 (21.3)	505 (44.4)	339 (67.1)	242 (71.4)
Patients who discontinued/dropped out, n (% of patients)	896 (78.7)	633 (55.6)	166 (32.9)	97 (28.6)
Reason for discontinuation, n (% of patients who discontinued/dropped out)				
Incomplete visits	434 (48.4)	314 (49.6)	67 (40.4)	53 (54.6)
Discontinued/dropped out*	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)

Adapted from Kato et al.[4] *Patients may have had more than one reason for discontinuing/dropping out.

CONCLUSIONS

- The safety, efficacy, and persistence of 3 years of treatment with mirabegron in patients with OAB symptoms were demonstrated in this clinical practice study
- **Safety:** mirabegron was well tolerated; reported ADRs were generally consistent with the known safety profile of mirabegron and no cumulative events or delayed ADRs were observed
- **Efficacy:** mirabegron was an effective treatment and early improvements in OABSS were maintained over the 3-year study. The majority of patients who positively responded to mirabegron in the first year continued to respond over the treatment period
- **Persistence:** high persistence was observed with mirabegron. Using the Kaplan–Meier method, approximately two-thirds of patients were persisting with treatment after 1 year and almost half were still receiving mirabegron after 3 years
- **Limitation:** while valuable data were acquired for patients receiving mirabegron, evaluations outside mirabegron use would have provided further useful real-world data

ACKNOWLEDGMENTS

This study was funded by Astellas Pharma Inc. Medical writing support was provided by Michael Parsons of Envision Scientific Solutions and funded by Astellas Pharma Global Development.

DISCLOSURES

All of the authors are employees of Astellas Pharma Inc.

REFERENCES

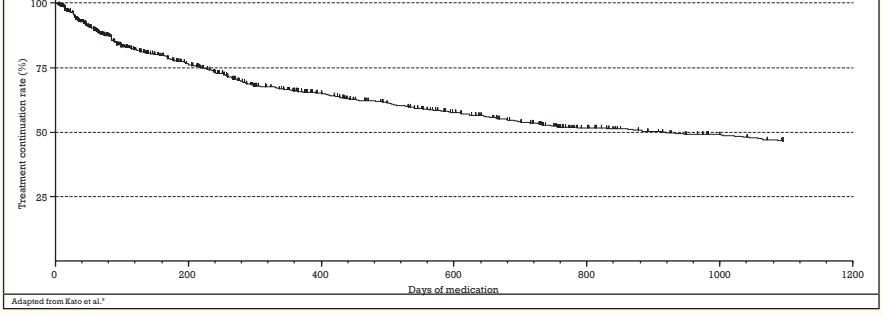
1. Vouri SM, Kebodeaux CD, Stranges PM, et al. *Arch Gerontol Geriatr* 2017; **69**: 77–96.
2. Yamaguchi O. *Neurourol Urodyn* 2010; **29**: 112–115.
3. Takasu T, Ukai M, Sato S, et al. *J Pharmacol Exp Ther* 2007; **321**: 642–647.
4. Yamaguchi O, Ikeda Y, Ohkawa S. *Low Urin Tract Symptoms* 2017; **9**: 38–45.
5. Wagg A, Franks B, Ramos B, et al. *Can Urol Assoc J* 2015; **9**: 343–350.
6. Nitti VW, Rovner ES, Franks B, et al. *Am J Pharm Benefits* 2016; **8**: e25–e33.
7. Kato D, Uno S, Van Schyndle J, et al. *Int J Urol* 2017; **24**: 757–764.
8. Kato D, Tabuchi H, Uno S. *Low Urin Tract Symptoms* 2017; doi: 10.1111/luts.12188.
9. Kato D, Tabuchi H, Uno S. *Low Urin Tract Symptoms* 2018; doi: 10.1111/luts.12237.
10. Japan Pharmaceutical Manufacturers Association. *Pharmaceutical Administration and Regulations in Japan, 2015*. Available at: http://www.jpma.or.jp/english/parj/pdf/2015.pdf. Last accessed: June 6, 2018.

Table 2. ADRs by time of onset (Safety Analysis Set)

Variable	Time period														Cumulative total
	<1 m	≥1–<3 m	≥3–<6 m	≥6–<9 m	≥9 m–<1 y	≥1 y–<1 y and 3 m	≥1 y and 3 m–<1 y and 6 m	≥1 y and 6 m–<1 y and 9 m	≥1 y and 9 m–<2 y	≥2 y–<2 y and 3 m	≥2 y and 3 m–<2 y and 6 m	≥2 y and 6 m–<2 y and 9 m	≥2 y and 9 m–<3 y	≥3 y	Unknown	
Patients, n	1138	1003	804	672	575	505	443	411	376	339	291	272	258	242	–	1138
Patients with ADRs, n	27	18	16	9	9	6	2	3	6	1	2	3	2	0	3	97
ADRs, n	30	19	17	10	9	6	3	3	6	1	2	3	2	0	3	109
Incidence of patients with ADRs, % of patients	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, n (% of 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)*	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)

Adapted from Kato et al.[4] *The ADR was reported by the investigator as "gastrointestinal symptom" with unknown specific symptoms.
ADR=adverse drug reaction

Figure 2. Overall patient persistence according to the Kaplan–Meier method



Adapted from Kato et al.[4]