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Safety and effectiveness of mirabegron in patients ≥75 years with overactive bladder: analysis of a Japanese post-marketing commitment study

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INTRODUCTION

- Prevalence of overactive bladder (OAB) increases with age
- In Japan, the proportion of elderly individuals within the total population is increasing[1]
- Mirabegron, a first-in-class, β_3-adrenoreceptor agonist has a more favourable tolerability profile and an improved benefit-to-risk ratio compared with antimuscarinics in patients with OAB aged ≥65 years[2,3]
- In a 12-week post-marketing study in Japanese patients with OAB initiating treatment with mirabegron in a routine clinical setting, 48.8% of the patients were aged ≥75 years[4]

OBJECTIVE

- To conduct a post hoc analysis of patients with OAB aged ≥75 years versus those aged <75 years to determine the safety and effectiveness of mirabegron in a routine clinical setting

METHODS

Study design

- Prospective, non-interventional, mono-arm survey (BE0001; ClinicalTrials.gov Identifier NCT01919047) conducted for a period of 12 weeks, in compliance with Japanese Good Post-Marketing Study Practice (GPSP)[5]
- Patients were stratified into two groups: aged ≥75 and <75 years
- Full medical histories including prior and concomitant drug use, were collected from patients before initiating mirabegron treatment

Patients

- Aged ≥75 years and <75 years who were prescribed mirabegron for treatment of OAB symptoms and who had not been previously treated with mirabegron

Safety assessment

- Adverse drug reactions (ADRs) were coded using the Japanese version of MedDRA (version 17.1) with incidence summarized by system organ class (SOC) and preferred term (PT)

Efficacy assessments

- At Baseline (BL) and end of treatment (EoT)
  - Physicians evaluated OAB symptoms and judged treatment as 'effective', 'ineffective', or 'not evaluable'
  - Patients completed the Overactive Bladder Symptom Score (OABSS) and the International Prostate Symptom Score-Quality of Life (IPSS-QoL) surveys
    - A reduction of 3 points in the total score was defined as minimal clinically important change (MCIC)
    - OAB symptom severity was classified as 'Mild' (OABSS: 0–5), 'Moderate' (OABSS: 6–11) or 'Severe' (OABSS: 12–15)
  - Patients completed the IPSS-QoL survey
    - QoL severity was classified as 'Mild' (score: 0 or 1), 'Moderate' (score: 2–4) or 'Severe' (score: 5 or 6)

Statistical analysis

- Post hoc analysis of patients with OAB aged ≥75 years versus those aged <75 years
- Safety Analysis Set (SAF): included patients who received ≥1 dose of mirabegron and had ≥1 study visit after initial administration
- Efficacy Analysis Set: included patients diagnosed with OAB and considered eligible for efficacy assessment by the attending physician
- OABSS Analysis Set: included patients from the Efficacy Analysis Set if they did not have concurrent diseases excluded for OAB diagnosis, were judged to have OAB based on the OABSS definition (OABSS question 3 score ≥2 points and total OABSS ≥3 points), received mirabegron according to the dosing regimen, and completed the OABSS at BL and EoT without missing values
- Statistical tests were two-sided and p<0.05 was defined as statistically significant

RESULTS

Patient disposition

- Between April 2012 and July 2014, survey data from 10,688 patients were collected from 1111 medical institutions
- SAF: 4784 patients aged ≥75 years and 5011 patients aged <75 years
- Efficacy Analysis Set: 4784 patients aged ≥75 years and 5008 patients aged <75 years
- OABSS Analysis Set: 1958 patients aged ≥75 years and 2195 patients aged <75 years

Demographic and baseline characteristics of patients

- In the SAF, 50.5% and 43.3% of patients aged ≥75 years and <75 years, respectively, were male (Table 1)
  - A significantly greater proportion of patients aged ≥75 years than those aged <75 years had higher prostate volume
- Significantly higher percentages of patients aged ≥75 years than those aged <75 years had:
  - Lower BMI
  - Longer OAB duration
  - More severe OAB symptoms
  - Incontinence
  - Increased residual urine volume
    - Significantly greater proportions of patients aged ≥75 years than those aged <75 years had higher residual urine volume
  - Concurrent diseases (Table 2)
    - Prostatic hyperplasia, hypertension, constipation, prostate cancer, angina pectoris, osteoporosis, and arrhythmia
  - Concomitant drug use
    - α_1 blockers, anticholinergic agents, and 5α-reductase inhibitors

Safety assessment

- Incidence of ADRs was low in both age groups, however, it was significantly higher in SAF patients aged ≥75 years than those <75 years (Table 3)
  - ≥75 years: 388 ADRs were reported in 335 of 4784 (7.00%) patients
  - <75 years: 294 ADRs were reported in 260 of 5011 (5.19%) patients
- Higher percentages of patients aged ≥75 years than those aged <75 years had residual urine volume increased, dysuria, thirst, dizziness, urinary retention, cystitis, and urinary tract infection
- Palpitations occurred at a higher incidence in patients aged <75 years than in those aged ≥75 years

Table 1. Patient characteristics (Safety Analysis Set)

		Patients, n (%)		
		Age <75 years (n=5011)	Age ≥75 years (n=4784)	p-value
Sex	Male	2170 (43.3)	2418 (50.5)	<0.001*
	Female	2841 (56.7)	2366 (49.5)	
Prostate volume (mL)	<20 mL	504 (23.2)	490 (20.3)	0.004†
	≥20 mL, <30 mL	469 (21.6)	508 (21.0)	
	≥30 mL, <40 mL	257 (11.8)	312 (12.9)	
	≥40 mL, <50 mL	125 (5.8)	162 (6.7)	
	≥50 mL	134 (6.2)	172 (7.1)	
	Unknown	681 (31.4)	774 (32.0)	n/a
BMI	<18.5	159 (3.2)	199 (4.2)	<0.001†
	≥18.5, <25.0	1434 (28.6)	1321 (27.6)	
	≥25.0, <30.0	494 (9.9)	404 (8.4)	
	≥30.0	109 (2.2)	55 (1.1)	
	Unknown	2815 (56.2)	2805 (58.6)	n/a
OAB duration	<3 months	1173 (23.4)	956 (20.0)	<0.001†
	≥3 months, <1 year	1156 (23.1)	1006 (21.0)	
	≥1 year, <3 years	1231 (24.6)	1153 (24.1)	
	≥3 years	1015 (20.3)	1179 (24.6)	
	Unknown	436 (8.7)	490 (10.2)	n/a
OAB severity‡	Mild	990 (19.8)	726 (15.2)	<0.001†
	Moderate	2833 (56.5)	2562 (53.6)	
	Severe	559 (11.2)	815 (17.0)	
	Unknown	629 (12.6)	681 (14.2)	n/a
Incontinence status§	Absent (DRY)	1415 (28.2)	1035 (21.6)	<0.001*
	Present (WET)	2977 (59.4)	3078 (64.3)	
	Unknown	619 (12.4)	671 (14.0)	n/a
Residual urine volume	<25 mL	2431 (48.5)	2217 (46.3)	<0.001†
	≥25 mL, <50 mL	598 (11.9)	596 (12.5)	
	≥50 mL, <100 mL	299 (6.0)	380 (7.9)	
	≥100 mL	73 (1.5)	68 (1.4)	
	Unknown	1610 (32.1)	1523 (31.8)	n/a

*Fisher's exact test. †Cochran-Armitage test. ‡Severity of total OABSS at Baseline. Mild (0–5), moderate (6–11), and severe (12–15). §Absent (DRY): OABSS Question 4 was 0 points at Baseline. Present (WET): OABSS Question 4 was ≥1 point at Baseline. BMI=body mass index; n/a=not applicable; OAB=overactive bladder; OABSS=Overactive Bladder Symptom Score

Table 2. Concurrent diseases and concomitant medication (Safety Analysis Set)

		Patients, n (%)		
		Age <75 years (n=5011)	Age ≥75 years (n=4784)	p-value
Concurrent disease	No	1624 (32.4)	988 (20.7)	<0.001*
	Yes	3305 (66.0)	3722 (77.8)	
	Unknown	82 (1.6)	74 (1.5)	
Concurrent disease present in ≥3.0% of patients aged ≥75 years	Prostatic hyperplasia	1398 (27.9)	1778 (37.2)	
	Hypertension	1350 (26.9)	1774 (37.1)	
	Diabetes mellitus	455 (9.1)	470 (9.8)	
	Hyperlipidemia	470 (9.4)	415 (8.7)	
	Constipation	149 (3.0)	247 (5.2)	
	Insomnia	152 (3.0)	227 (4.7)	
	Prostate cancer	71 (1.4)	221 (4.6)	
	Angina pectoris	86 (1.7)	211 (4.4)	
	Osteoporosis	100 (2.0)	204 (4.3)	
	Arrhythmia	95 (1.9)	203 (4.2)	
	Glaucoma	136 (2.7)	173 (3.6)	
Medical history	No	3324 (66.3)	2769 (57.9)	<0.001*
	Yes	1233 (24.6)	1386 (29.0)	
	Unknown	454 (9.1)	629 (13.1)	n/a
Concomitant medication	No	2425 (48.4)	1842 (38.5)	<0.001*
	Yes	2439 (48.7)	2789 (58.3)	
	Unknown	147 (2.9)	153 (3.2)	
Drug categories present in ≥3.0% of patients aged ≥75 years	α1-antagonist	1208 (24.1)	1512 (31.6)	
	Anticholinergic	276 (5.5)	345 (7.2)	
	5α-reductase inhibitor	117 (2.3)	210 (4.4)	
Drug specified and present in ≥2.0% of patients aged ≥75 years	Amlodipine besylate	219 (4.4)	276 (5.8)	
	Magnesium oxide	83 (1.7)	132 (2.8)	
	Aspirin	66 (1.3)	129 (2.7)	

*Fisher's exact test. n/a=not applicable

Table 3. Incidence of adverse drug reactions (Safety Analysis Set)

Incidence of ADRs*	Patients, n (%)	
	Age <75 years (n=5011)	Age ≥75 years (n=4784)
Any ADR, n (%)	260 (5.19)	335 (7.00)
Common ADRs present in ≥0.1% of patients ≥75 years, events (%)		
Constipation	47 (0.94)	48 (1.00)
Residual urine volume increased	30 (0.60)	40 (0.84)
Dysuria	18 (0.36)	25 (0.52)
Thirst	21 (0.42)	25 (0.52)
Dizziness	5 (0.10)	22 (0.46)
Urinary retention	9 (0.18)	21 (0.44)
Cystitis	9 (0.18)	15 (0.31)
Abdominal discomfort	13 (0.26)	11 (0.23)
Diarrhoea	11 (0.22)	11 (0.23)
Nausea	10 (0.20)	8 (0.17)
Headache	4 (0.08)	6 (0.13)
Hypertension	3 (0.06)	6 (0.13)
Pruritus	6 (0.12)	6 (0.13)
Urinary tract infection	0	6 (0.13)
Urticaria	4 (0.08)	6 (0.13)
Abdominal distension	2 (0.04)	5 (0.10)
Abdominal pain lower	3 (0.06)	5 (0.10)
Palpitations	12 (0.24)	5 (0.10)

*Japanese MedDRA version 17.1. ADRs=adverse drug reactions

Efficacy

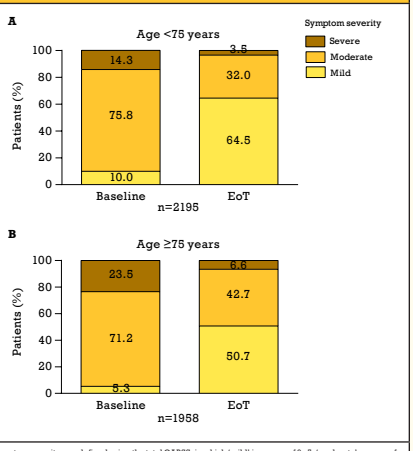
- Mirabegron treatment was reported as 'effective' by the physician in 79.3% of patients ≥75 years, which was significantly lower than the efficacy rate of 82.1% in patients aged <75 years (Table 4)
- OABSS
  - Change from BL to EoT in patients aged ≥75 years was significantly lower than that in patients aged <75 years (Table 4)
  - 61.0% and 65.9% patients aged ≥75 years and <75 years, respectively, achieved MCIC
  - Compared with BL, the percentage of patients with less severe symptoms was statistically significantly higher in both age groups at EoT (Figure 1)
- IPSS-QoL
  - Change from BL to EoT in patients aged ≥75 years was statistically significantly lower than that in patients aged <75 years (Table 4)
  - Compared with BL, the percentage of patients with less severe symptoms was statistically significantly higher in both age groups at EoT (Figure 2)

Table 4. Mirabegron treatment efficacy

	Age <75 years	Age ≥75 years
Effectiveness		
n*	4815	4579
'Effective', n (%)	3952 (82.1)	3630 (79.3)
'Not effective', n (%)	863 (17.9)	949 (20.7)
OABSS		
n†	2195	1958
BL [mean (SD)]	8.6 (2.49)	9.5 (2.50)
EoT [Mean (SD)]	4.8 (3.09)	5.9 (3.32)
Change by EoT [mean (SD)]	-3.8 (3.01)	-3.6 (3.22)
Test‡	<0.001	<0.001
Intergroup comparison§	Reference	0.002
MCIC achieved, n (%)	1447 (65.9)	1194 (61.0)
Test¶	Reference	<0.001
IPSS-QoL		
n**	2028	1805
BL [mean (SD)]	5.0 (0.90)	4.9 (0.97)
EoT [Mean (SD)]	2.8 (1.63)	2.9 (1.58)
Change by EoT [mean (SD)]	-2.2 (1.76)	-2.0 (1.77)
Test‡	<0.001	<0.001
Intergroup comparison§	Reference	<0.001

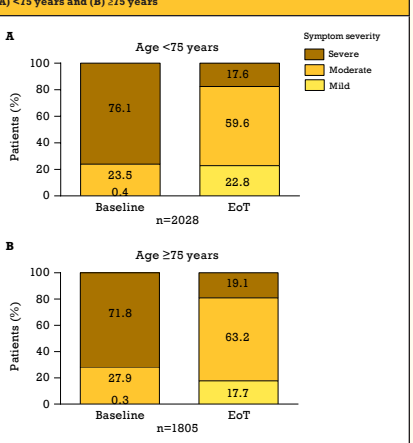
*Excluding patients in the Efficacy Analysis Set who were not evaluable. †OABSS Analysis Set. ‡Wilcoxon signed-rank test. §Wilcoxon rank sum test. ¶Fisher's exact test. **Patients in the OABSS Analysis Set whose IPSS-QOL data were available. BL=Baseline; EoT=end of treatment; IPSS-QoL=International Prostate Symptom Score-Quality of Life; MCIC=minimal clinically important change; OABSS=Overactive Bladder Symptom Score; SD=standard deviation

Figure 1. Change from baseline to end of treatment in overactive bladder symptom severity in patients in the OABSS Analysis Set aged (A) <75 years and (B) ≥75 years



Symptom severity was defined using the total OABSS, in which 'mild' is a score of 0–5, 'moderate', a score of 6–11, and 'severe', a score of 12–15. EoT=end of treatment; OABSS=Overactive Bladder Symptom Score

Figure 2. Change from baseline to end of treatment in severity of QoL as measured by IPSS-QoL score in patients in the OABSS Analysis Set aged (A) <75 years and (B) ≥75 years



QoL severity was defined as 'mild', a score of 0 or 1, 'moderate', a score of 2–4, or 'severe', a score of 5 or 6. EoT=end of treatment; IPSS-QoL=International Prostate Symptom Score-Quality of Life; OABSS=Overactive Bladder Symptom Score; QoL=quality of life

CONCLUSIONS

- In a real-world clinical setting, mirabegron was well tolerated and effective in patients aged ≥75 years and <75 years

ACKNOWLEDGEMENTS

This study was funded by Astellas Pharma Inc. Japan. Editorial assistance was provided by Nibedita Gupta of Envision Scientific Solutions and funded by Astellas Pharma Global Development. The authors would like to thank the Contract Research Organisation EPS Corporation.

DISCLOSURES

MY received grants and personal fees from Astellas. YN, DK, HT and KK are employees of Astellas Pharma Inc.

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Presented at the 47th Annual Meeting of the International Continence Society, September 12–15, 2017, Florence, Italy