Original Article - Lower Urinary Tract Dysfunction

Investig Clin Urol 2025;66:27-35.
https://doi.org/10.4111/icu.20240278
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY

Multi-center, prospective, non-interventional, observational study on the efficacy and safety of Mirabek® in adult patients with overactive bladder

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Purpose: Mirabegron, the first-in-class beta-3 agonist, is the mainstay medication for overactive bladder (OAB). The aim of this study was to investigate the efficacy and safety of generic drugs of mirabegron (Mirabek®) in adults diagnosed with OAB through a multicenter, prospective, non-interventional observational study.

Materials and Methods: Adult patients with OAB prescribed Mirabek® SR Tab. 50 mg for the first time were recruited from hospitals between September 2021 and September 2022. Participants underwent baseline registration followed by two follow-ups at 4- and 8-week intervals. Data on demographics, medical history, OAB symptoms, vital signs, medication administration, and adverse events were collected.

Results: Among 1,714 patients, Mirabek® SR Tab. 50 mg effectively improved OAB symptoms over an 8-week treatment period, with significant differences in symptom improvement between baseline and both 4- and 8-week time points as well as between 4 weeks and 8 weeks. The incidence rate of adverse events was 0.70%; most cases were mild with no severe reactions.

Conclusions: This study demonstrated that Mirabek®, a generic drug of betmiga, is an effective and safe treatment option for adults with OAB. Furthermore, the introduction of generic drug reduced the costs of prescription drugs and expanded the opportunity for many patients to access mirabegron.

Keywords: Adrenergic beta-3 receptor agonists; Mirabegron; Urinary bladder, overactive

INTRODUCTION

The prevalence of overactive bladder (OAB), a subtype of lower urinary tract syndrome that manifests with symptoms such as urinary urgency, is estimated to affect 10%–15% of the population [1,2], as outlined by the International Continence Society [3]. OAB management strategies typically encompass behavioral therapy and medical management [4,5], with anticholinergics and beta-3 agonists being the mainstay medications for OAB [4,6]. Anticholinergics inhibit bladder smooth muscle contractions induced by acetylcholine, thereby promoting relaxation. Despite their established efficacy and safety profile over prolonged periods, anticholinergics are associated with side effects such as dry mouth, constipation, dizziness, blurred vision, dementia, and headaches [7-11]. Additionally, their non-selective actions on the bladder

Received: August 7, 2024 • **Revised:** September 9, 2024 • **Accepted:** October 23, 2024 • **Published online:** December 20, 2024
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smooth muscle may lead to adverse events such as increased residual urine volume and acute urinary retention.

Beta-3 agonists have a distinct mechanism of action. Mirabegron, the first-in-class beta-3 agonist, activates beta-3 adrenergic receptors to induce bladder muscle relaxation [12,13]. It acts on not only the bladder, but also urothelial and afferent nerves, potentially influencing bladder relaxation [12,13]. Clinical guidelines recommend mirabegron as the first-line treatment option along with anticholinergics owing to its efficacy in symptom improvement and notably fewer side effects, particularly dry mouth [14,15].

Using generic drugs rather than brand-name drugs has been identified as a crucial strategy to manage the increasing costs of prescription drugs [16,17]. Generic drugs are bioequivalent to their reference listed drugs, containing the same active ingredients, but are priced 80%–85% lower than branded versions [18]. Mirabek® is a generic drug of Betmiga® (Astellas Pharma Inc.) manufactured by Hanmi Pharmaceutical Co., Ltd., and it accounts for a large part of mirabegron sales in Republic of Korea. Despite its availability, there is no real-world data regarding the efficacy and safety of Mirabek® in treating OAB. Furthermore, large-scale observational studies targeting the Korean OAB population are lacking. Additionally, post-marketing surveillance studies on other drugs containing mirabegron have predominantly focused on long-term safety rather than comprehensively evaluating its therapeutic effects. At last, most importantly, we have evaluated how the introduction of generic drug, Mirabek®, changed the drug use and spending in Korean mirabegron pharmaceutical market. Therefore, the aim of this study was to address the lack of real-world evidence by assessing the treatment efficacy and safety of Mirabek® in Korean adult patients with OAB, thereby contributing valuable insights regarding its clinical use in domestic practice and the economic impact by the introduction of the generic drug of mirabegron in Korea

MATERIALS AND METHODS

1. Study design

In this multi-center, prospective, non-interventional observational study, we evaluated the efficacy and safety of a 50-mg mirabegron sustained-release tablet (Mirabek® SR Tab. 50 mg) in adult patients with OAB in real-world clinical settings. This study has been performed only in local clinics.

2. Ethics statement

This present study protocol was reviewed and approved by the Public Institutional Review Board Designated by the Ministry of Health and Welfare (approval number: P01-202108-21-012). The study was performed in accordance with approved guidelines and regulations for medical research in the Declaration of Helsinki (2013). Participation was voluntary, and informed consent was obtained by all subjects.

3. Participants

Patients visiting hospitals between September 2021 and September 2022 were recruited. The inclusion criteria were participants diagnosed with OAB and prescribed Mirabek® SR Tab. 50 mg for the first time based on the medical judgment of clinicians. Patients who were treated with Mirabek® SR Tab. 50 mg or switched from another OAB medication to Mirabek® SR Tab. 50 mg were also included.

4. Intervention

Mirabek® SR Tab. 50 mg was administered orally once daily according to the approved indication for adults, including elderly individuals. Participants were instructed to take the medication with or without food, swallow the whole tablet with water, and avoid chewing or crushing.

5. Study flow

This observational study did not involve any intervention beyond routine clinical care. Participants underwent two follow-up visits at 4- and 8-week intervals from baseline registration (±2 weeks), and prospective data were collected (Fig. 1). During these visits, investigators collected necessary data as part of routine OAB management. Participants who did not visit the clinic during these intervals were followed up via telephone.

6. Outcome measures

The primary outcome was to assess the improvement in OAB symptoms 8 weeks after initiating Mirabek® SR Tab. 50 mg treatment compared with those at baseline using the total OAB symptom score (OABSS). The secondary outcome included evaluating the efficacy of Mirabek® SR Tab. 50 mg treatment at 4 weeks and assessing its safety profile.

7. Inclusion and exclusion criteria

The inclusion criteria included adults aged 19 years and older diagnosed with OAB who were prescribed Mirabek® SR Tab. 50 mg for the first time and voluntarily consented to participate. The exclusion criteria included patients with hypersensitivity to the main ingredient or other components of this medication, severe uncontrolled hypertension (systolic blood pressure [BP] ≥180 mmHg and/or diastolic BP ≥110 mmHg), severe cardiac disorders, pregnancy or breastfeeding,

https://doi.org/10.4111/icu.20240278

Fig. 1. Study flowchart. Tab., tablet; W, week.

Table 1. Study schedule

	Visit 1	Visit 2	Visit 3
	Baseline	4W±2W	8W±2W
Informed consent form	O	-	-
Inclusion & exclusion criteria	O	-	-
Demographics	O	-	-
Medical history	O	-	-
OAB-related information	O	-	-
OABSS	O	O	O
Vital signs	O	O	O
Medication administration information	O	O	O
Adverse events reporting	-	O	O

W, week; OAB, overactive bladder; OABSS, OAB symptom score.

and other factors rendering the patient unsuitable for study participation.

8. Data collection

After completing the recruitment procedure, demographic and medical data, OABSS, vital signs, medication use details, and adverse events were collected as per the study schedule (Table 1). Detailed information is outlined below.

1) Demographics
   (1) Sex, date of birth, age (in years), height, weight, and body mass index
   (2) Lifestyle factors: Alcohol consumption (non-drinker, past drinker, or current drinker), smoking status (non-smoker, former smoker, or current smoker)
   (3) Reproductive history: Pregnancy and lactation status
2) Medical history: Diagnoses of severe liver disorders and allergies at baseline
3) OAB-related information: Detailed OAB diagnosis, date of diagnosis, total duration of illness, and history of surgeries. Preceding medications for OAB (information on medications related to OAB taken within 3 months prior to enrollment. Reasons for prescription changes in cases of prior anticholinergic or mirabegron agent use were also documented.).
4) OABSS: Scores were recorded at each visit using standardized OABSS questionnaires. OAB severity was classified as "mild" (total OABSS 0–5), "moderate" (total OABSS 6–11), and "severe" (total OABSS 12–15).
5) Vital signs: Vital signs such as systolic/diastolic BP and heart rate were measured at each visit. Baseline measurements were taken before the administration of any study medications.
6) Medication administration information: Dosage frequency, duration of administration (start and end dates), any treatment modifications or discontinuation, related reasons, and concomitant medication use.
7) Adverse event and adverse drug reaction reporting: All adverse events and adverse drug reaction occurring from the first administration of Mirabek® SR Tab. 50 mg until study completion or participant dropout were recorded. Every undesirable and unintended signs (e.g., abnormal laboratory test results), symptoms or diseases that occurred in the subjects during the administration of the drug was monitored. Adverse events and adverse drug reactions were classified by the system organ class (SOC) and preferred term (PT) of Medical Dictionary for Regulatory Activities (MedDRA) version 26.0.

9. Statistical analysis

Analysis of baseline characteristics was conducted for the safety analysis set. Descriptive statistics are used to summarize demographic characteristics, medical history, medication usage, vital signs, OABSS, and adverse events. Continuous variables are reported as mean±standard deviation and categorical variables are presented as frequency and percentage. For efficacy assessment, improvement in OAB symptoms at 8 weeks post-treatment compared with those at baseline was primarily evaluated. The number and percentage (%) of participants showing an improvement of at least 3 points in total OABSS from baseline to 8 weeks post-treatment are reported along with their respective two-sided 95% confidence intervals. For secondary analysis,

improvement in OAB symptoms at 4 weeks post-treatment was compared with those at baseline. The number and percentage (%) of participants showing an improvement of at least 3 points in total OABSS from baseline to 4 weeks post-treatment are reported along with their respective two-sided 95% confidence intervals. Safety was evaluated in terms of changes in vital signs (BP and heart rate) at each time point compared with those at baseline. Descriptive statistics (number of participants, mean, standard deviation, median, minimum, and maximum) are provided for continuous data related to vital signs at each time point and changes from those at baseline. Paired t-test or Wilcoxon signed-rank test was conducted for changes from baseline at each time point, and McNemar's test was conducted for changes within the treatment group. Incidence of adverse events over 8 weeks from baseline was recorded and classified according to the Medical Dictionary for Regulatory Activities latest version into SOC and PT. The occurrence of adverse events is summarized as number of participants, incidence rate, and number of occurrences for each adverse event type. The severity, course, and causality of adverse events are described. Pearson's chi-square test or Fisher's exact test was used to assess the statistically significant occurrence of adverse events by participant demographic factors. Multivariate analysis was conducted, considering the structure and characteristics of the collected data, to identify factors influencing the occurrence of adverse events. Statistical analysis was performed using IBM SPSS Statistics version 19.0 (IBM Corp.).

RESULTS

In this study, 1,880 patients who met the inclusion/exclusion criteria were enrolled. Of these, 1,844 participants were included in the safety analysis set. In the safety analysis set, 1,714 participants who had valid efficacy evaluation results at least once after the baseline visit were included in the full analysis set. Among 1,880 patients, a total of 131 patients either discontinued or dropped out, with the most common reason being 'loss to follow-up,' accounting for 99 patients. The mean total duration of administration for Mirabek® SR Tab. 50 mg was 59.42±14.03 days and the mean total dose administered was 2,970.91±701.57 mg.

In terms of efficacy of OAB symptom improvement at 4 weeks and 8 weeks compared with those at baseline in the full analysis set, the proportion of participants showing improvement in OAB symptoms after 4 weeks of Mirabek® SR Tab. 50 mg administration compared with those at baseline was 43.29% (742/1,714 participants) and that after 8 weeks was 66.74% (1,144/1,714 participants) (Fig. 2).

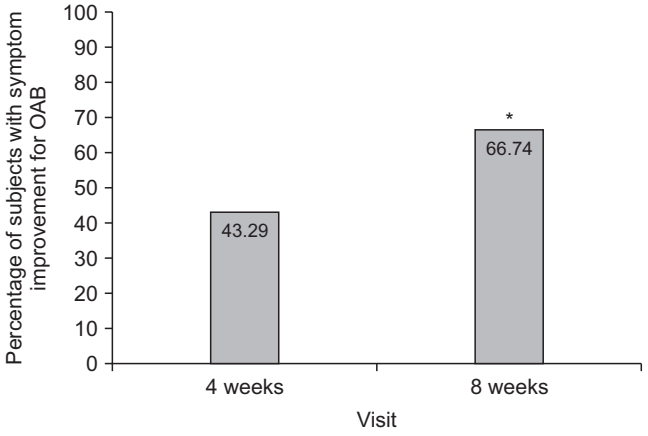

Fig. 2. Proportion of patients experiencing improvements in overactive bladder (OAB) symptoms at 4 weeks and 8 weeks after treatment compared with those at baseline. The asterisk (*) denotes significant differences between 4 weeks and 8 weeks using McNemar's test ($p<0.0001$).

We observed significant improvements in OAB symptoms following the administration of Mirabek® SR Tab. 50 mg at both 4- and 8-week time points compared with those at baseline ($p<0.0001$). Furthermore, there was a significant difference in symptom improvement between the 4- and 8-week time points ($p<0.0001$). Analysis of the severity of OAB symptoms according to the OABSS classification revealed a progressive increase in the proportion of patients categorized as "mild" from baseline (29.70% or 509 out of 1,714 patients) to 4 weeks (59.16% or 1,014 out of 1,714 patients) and 8 weeks (78.47% or 1,345 out of 1,714 patients). The differences in severity between baseline and 4 weeks and between baseline and 8 weeks were significant ($p<0.0001$) (Fig. 3).

Significant reductions were observed in the total OABSS from baseline to the 4-week and 8-week time points, with mean changes of -2.45±2.02 and -3.90±2.49 points, respectively. Additionally, a significant mean change of -1.48±1.56 points was noted from the 4- to 8-week time points ($p<0.0001$). These findings demonstrate a progressive decrease in OAB symptom severity over the treatment period, with significant differences observed between baseline and both follow-up time points.

In terms of safety, among the 1,844 participants in the safety analysis set, 13 experienced adverse events, with a total of 14 cases. The incidence rate of adverse events was 0.70%, with adverse drug reactions accounting for 0.49% of cases. The detail adverse events and adverse drug reactions are listed in Supplementary Table 1. The severity of all reported adverse events was "mild," and no severe adverse events or reactions were observed.

Regarding vital signs, a significant decrease in systolic

https://doi.org/10.4111/icu.20240278

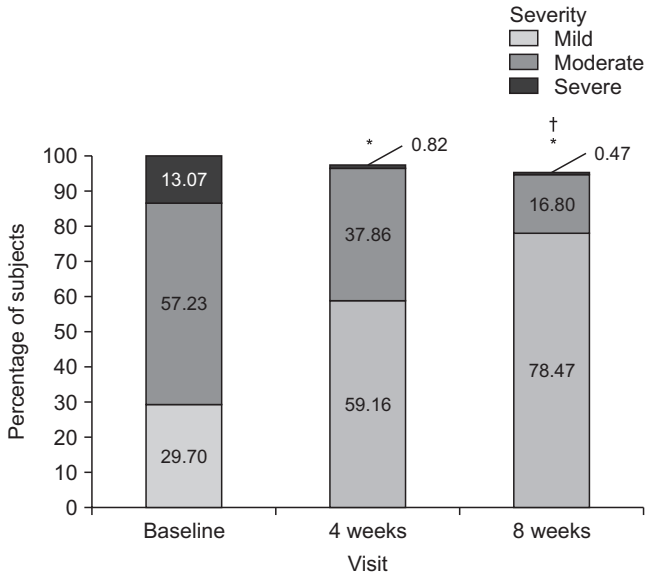

Fig. 3. Proportion of patients stratified by overactive bladder (OAB) symptom severity according to the total OAB symptom score (OABSS) (total OABSS 0–5, mild; 6–11, moderate; 12–15, severe) after treatment. The asterisks (*) denote significant differences between 4 weeks and 8 weeks compared to baseline using McNemar's test ($p<0.0001$). The dagger (†) denotes significant differences between 4 weeks and 8 weeks using McNemar's test ($p<0.0001$).

and diastolic BPs was observed from baseline to the 4-week and 8-week time points in among approximately 20% of patients in the safety analysis set. However, caution is warranted in generalizing these results to the entire safety analysis set owing to the subset analyzed. Overall, our results indicate the efficacy of Mirabek® SR Tab. 50 mg in reducing OAB symptoms over the 8-week treatment period with a favorable safety profile.

Before the introduction of the generic drug of mirabegron in Korea, the brand name drug, Betmiga®, has accounted for 100% of all prescription of mirabegron. Betmiga® accounted for total prescription volumes of 84.8 million tablets and total sales of 64.7 billion Korean won (KRW) per year (Table 2). After the introduction of generic drugs in 2020, the total prescription volume and sales increased to 102.2 million tablets and 71.2 billion KRW, respectively, showing a 20.5% growth in prescription volume (Table 2). After 4 years of the introduction of generic drug, Mirabek®, the total prescription volume increased more than two times, but the total sales remained similar (Table 2). This is due to the reduction of the costs of drug. Initially, Betmiga® was launched in Korea at 861 KRW per tablet, but following the emergence of generics, the price dropped to 381 KRW per tablet in 2021 and is currently sold at 360 KRW per tablet.

Table 2. The pharmaceutical market of mirabegron in Korea

Product name	Distributor	Prescription indicator	Year				
			2019	2020	2021	2022	2023
Mirabek®	Hanmi Pharmaceutical Co., Ltd.	Sales (KRW, billion)	0.0	3.0	11.8	13.3	15.6
		Volume (tablet, million)	0.0	60.0	25.1	34.8	41.0
Betmiga®	Astellas Pharma Inc.	Sales (KRW, billion)	64.7	67.4	60.4	32.2	32.5
		Volume (tablet, million)	84.8	93.7	94.5	89.6	90.6
Mirabegron total		Sales (KRW, billion)	64.7	71.2	76.1	55.2	66.3
		Volume (tablet, million)	84.8	102.2	129.7	151.9	184.1
Year-over-year prescription volume growth rate (%)				+20.5	+26.9	+17.1	+21.2

KRW, Korean won.

DISCUSSION

This study provides important insights into the efficacy and safety of Mirabek® SR Tab. 50 mg, a generic drug of betmiga, in managing OAB symptoms in adult patients. The findings suggest that Mirabek® SR Tab. 50 mg is effective in improving OAB symptoms over an 8-week treatment period, with a progressively increasing proportion of participants experiencing symptom improvement with extension in the treatment duration. This observation was supported by significant differences in symptom improvement between baseline and both 4- and 8-week time points as well as between 4 weeks and 8 weeks. The observed reduction in OAB symptom severity, as indicated by changes in OABSS from baseline to 4 weeks and 8 weeks, further reinforces the efficacy of Mirabek® SR Tab. 50 mg in managing OAB. The progressive decrease in symptom severity over the treatment period underscores the sustained benefit of Mirabek® SR Tab. 50 mg in alleviating OAB symptoms.

Multiple randomized controlled trials have reported that mirabegron monotherapy significantly improves OAB symptoms compared to placebo in terms of daily urinary frequency, incontinence episodes, volume voided per miction, and urgency episodes supported by several systematic reviews and meta-analyses [15,19-22]. Here, the low incidence of adverse events, all of which were mild, highlights the favorable safety profile of Mirabek® SR Tab. 50 mg. Notably, no severe adverse events or reactions were reported, indicating that Mirabek® SR Tab. 50 mg is well-tolerated in adults with OAB. Mirabegron, owing to its distinct mechanism of action, is expected to have a markedly different adverse event profile compared to anticholinergics. Multiple trials have shown that mirabegron monotherapy offers the advantage of exhibiting lower levels of anticholinergic symptoms [21-23] such as xerostomia and constipation, which are common reasons for poor long-term compliance with anticholinergics [24]. Initially, there were concerns regarding the effect of beta-3 agonists on the cardiovascular system (CVS) owing to the presence of beta-adrenergic receptors in the heart and blood vessels [25,26]. However, long-term safety data on mirabegron have not demonstrated clinically significant disturbances in the CVS [23]. Our study demonstrated a significant decrease in both systolic and diastolic BPs in 20% of the study participants. Although mirabegron is already known to be safely used with minimal fluctuations in BP and pulse rate, elevated BP was observed in some patients [27]. Overall, in addition to previous studies, our study demonstrates that mirabegron is a safe option for the treatment of OAB, with the main advantage of reduced incidence of anticholinergic-induced adverse events. Furthermore, mirabegron formulations, including Mirabek® SR Tab. 50 mg, have shown short- and long-term CVS safety profiles with no effect on pulse rate or BP.

As the purpose of generic drug, entry of Mirabek® in Korean mirabegron pharmaceutical market successfully reduced the costs of prescription drugs and expanded the opportunity for many patients to access mirabegron. Although it has been only 4 years of the introduction of Mirabek®, the total prescription volume doubled, but the total sales remained similar. This clear demonstrates the need of generic drug in terms of cost savings. However, we should not neglect sufficient incentives to encourage continued medical innovation through the development of new drugs [28].

In this study, among previous OAB medication users, all groups showed a significant improvement in OAB symptoms after the use of Mirabek® SR Tab. 50 mg. Even the group that previously used a mirabegron formulation other than Mirabek® SR Tab. 50 mg showed a two-fold improvement in OAB symptoms after the use of Mirabek® SR Tab. 50 mg. Although Mirabek® is a generic drug of betmiga, the exact composition of the drug is slightly different, which could explain its varying therapeutic effects. Therefore, we should further investigate this profile.

Our study further strengthens the effectiveness and safety of Mirabek® SR Tab. 50 mg, a generic drug of betmiga, in real-world clinical practice in the Republic of Korea. By demonstrating the efficacy and safety of Mirabek® SR Tab. 50 mg in a large cohort of adult patients with OAB, this study provides valuable clinical data that can inform treatment decisions and improve patient care.

This study has several strengths. First, this study included a large number of patients from 85 institutions, enhancing the generalizability of findings to a broader population of adult patients with OAB. Second, it was conducted in routine real-world clinical settings, providing valuable insights into its use beyond controlled trial conditions. Third, owing to the prospective nature of the study, it enabled the collection of data in real-time, minimizing recall bias and improving the reliability of the findings. Nevertheless, it is important to acknowledge certain limitations of this study. First, since this was an observational study, it does not fully represent real-life conditions and is susceptible to biases such as selection bias, confounding variables, and lack of randomization, which may limit the ability to establish causal relationships between Mirabek® SR Tab. 50 mg and the observed outcomes. Second, since the study duration was limited to 8 weeks, long-term efficacy and safety outcomes remain inconclusive, as most studies of this type evaluate

https://doi.org/10.4111/icu.20240278

outcomes over at least 6 months. Therefore, future research, including randomized controlled trials with longer follow-up periods, may provide additional insights into the sustained efficacy and safety of Mirabek® SR Tab. 50 mg in OAB management. Third, although decreased BP was observed in some study participants, as BP was not the main objective of this study, we should be cautious in interpreting the results of single point BP measure. Fourth, due to the study design of local clinics, we have to consider the differences in measuring equipment between individual local clinic and facilitate easier participation of clinical trials in local clinics. Therefore, this study only included the outcomes that are simple to measure and could not measure data such as functional bladder capacity, voided volume, residual urine volume, and incontinence episodes and long-term follow-up was not possible. Ongoing study performed in general hospital will report some of those data with long-term follow-up in the future publication. Fifth, the information of benign prostatic hyperplasia (BPH) is missing in this study. Recent studies reported the use of mirabegron in men with OAB and BPH to be effective with few adverse side effects [29]. Future studies will incorporate the data regarding BPH and will evaluate the efficacy and safety of generic drug in BPH. Sixth, although we presented the pharmaceutical market of mirabegron in Korea, this study is not a cost-analysis, so we cannot compare the economic benefits of generic drugs in the Korean mirabegron market.

CONCLUSIONS

Based on the findings of this study, Mirabek® SR Tab. 50 mg is as an effective and well-tolerated treatment option for OAB. As a representative agent targeting the beta-3 adrenergic receptor, it holds promise in achieving treatment goals in OAB management. The demonstrated efficacy of Mirabek® SR Tab. 50 mg in improving OAB symptoms, as evidenced by the significant improvement in symptoms and reductions in symptom severity over the 8-week treatment period, underscores its potential as a valuable therapeutic option. Furthermore, its favorable safety profile, with a low incidence of mild adverse events and no severe adverse reactions, enhances its appeal as a treatment choice for patients with OAB.

CONFLICTS OF INTEREST

Moon-Hwa Park is an employee of Hanmi Pharmaceutical Co., Ltd. Jee Soo Park is supported by a grant from the Hanmi Pharmaceutical Co., Ltd., which had no influence on the present work. The other authors have nothing to disclose.

FUNDING

This study was supported by the Hanmi Pharmaceutical Co., Ltd. and National Research Foundation of Korea (NRF) grants funded by the Korean Government (MSIT) (grant numbers: 2019R1A2C1002863 and 2022R1A2C2003831).

AUTHORS' CONTRIBUTIONS

Research conception and design: Jee Soo Park. Data acquisition: Jee Soo Park. Statistical analysis: Jee Soo Park. Data analysis and interpretation: Jee Soo Park. Drafting of the manuscript: Jee Soo Park. Critical revision of the manuscript: Jee Soo Park. Obtaining funding: Moon-Hwa Park and Won Sik Ham. Administrative, technical, or material support: Moon-Hwa Park and Won Sik Ham. Supervision: Jongchan Kim and Won Sik Jang. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20240278.

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