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Efficacy and Safety of Mirabegron and Tamsulosin Combination Therapy Compared to Tamsulosin Monotherapy for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: Results of a Multicenter, Randomized, Double-Blind, Phase III Clinical Trial

Sung Chul Kam[1,2,*], Yu Seob Shin[3,*], Doo sang Kim[4], Won Ki Lee[5], Deok Hyun Han[6], Phil Hyun Song[7], Sung Hoo Hong[8], Young Seop Chang[9], Tae Hwan Kim[10], Sung Tae Cho[11], Sung Yul Park[12], Jae Hyun Bae[13], Kyung Jin Chung[14], Joon Hwa Noh[15], Kang Su Cho[16], Tae Nam Kim[17], Zhao Luo[18], Won Sik Ham[19], Tae Hyo Kim[20]

[1]*Department of Urology, Gyeongsang National University College of Medicine and Institute of Health Sciences of Gyeongsang National University, Jinju, Korea,* [2]*Department of Urology, Gyeongsang National University Changwon Hospital, Changwon, Korea,* [3]*Department of Urology, Jeonbuk National University Medical School, Research Institute of Clinical Medicine of Jeonbuk National University-Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Korea,* [4]*Department of Urology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University School of Medical, Cheonan, Korea,* [5]*Department of Urology, Hallym University Chuncheon Sacred Heart Hospital, Hallym University School of Medical, Chuncheon, Korea,* [6]*Department of Urology, Sungkyunkwan University School of Medicine, Seoul, Korea,* [7]*Department of Urology, Yeungnam University College of Medicine, Daegu, Korea,* [8]*Department of Urology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea,* [9]*Department of Urology, Baekje General Hospital, Daejeon, Korea,* [10]*Department of Urology, Kyungpook National University School of Medicine, Daegu, Korea,* [11]*Department of Urology, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea,* [12]*Department of Urology, Hanyang University College of Medicine, Seoul, Korea,* [13]*Department of Urology, Korea University Ansan Hospital, Ansan, Korea,* [14]*Department of Urology, Gachon University Gil Medical Center, Incheon, Korea,* [15]*Department of Urology, Kwangju Christian Hospital, Kwangju, Korea,* [16]*Department of Urology, Prostate Cancer Center, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea,* [17]*Department of Urology, Pusan National University Hospital, Pusan National University School of Medicine, Biomedical Research Institute, Busan, Korea,* [18]*Department of Urology, Shenzhen Qianhai Taikang Hospital, Shenzhen, China,* [19]*Department of Urology and Urological Science Institute, Yonsei University College of Medicine, Seoul, Korea,* [20]*Department of Urology, Dong-A University Hospital, Dong-A University School of Medical, Busan, Korea*

Purpose: This study aimed to evaluate the efficacy and safety of mirabegron and tamsulosin combination therapy compared to tamsulosin monotherapy in benign prostatic hyperplasia (BPH) patients with lower urinary tract symptoms (LUTS).

Materials and Methods: This phase 3, randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy and safety of mirabegron/tamsulosin combination therapy versus tamsulosin monotherapy in men with LUTS. The trial, conducted across 25 centers from July 2021 to October 2023. Eligible participants were randomly assigned to either the combination or monotherapy group for 12 weeks. Primary efficacy endpoints included changes in total urinary frequency score (TUFS) and International Prostate Symptom Scores (IPSS), with secondary endpoints evaluating various urinary symptoms and changes in

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Correspondence to: Tae Hyo Kim https://orcid.org/0000-0002-5994-7878
Department of Urology, Dong-A University Hospital, 26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea.
Tel: +82-51-240-2727, **Fax:** +82-51-253-0591, **E-mail:** dockim0927@hanmail.net
*These authors contributed equally to this work as co-first authors.

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post void residual volume (PVR), maximum urinary flow rate (Qmax), and quality of life scores. Safety assessments included adverse events, PVR, Qmax, vital signs, electrocardiogram, and laboratory tests.

Results: A total of 795 participants were randomized to monotherapy (n=397) and combination therapy (n=398) groups. After 12 weeks, 342 in the monotherapy and 339 in the combination therapy group completed the study, with no significant baseline differences. The combination therapy group showed a greater improvement in TUFS (-11.28) and IPSS (-10.85) scores compared to monotherapy (-8.30 and -9.85, respectively) with significant differences (p<0.0001, p=0.0325). Combination therapy showed significant improvements in storage symptoms and voiding diary variables, including daytime frequency, urgency, and incontinence, compared to monotherapy. The incidence of treatment-emergent adverse events was similar between the groups (13.10% *vs* 16.58%, p=0.1943), with no serious drug-related adverse events, confirming an acceptable safety profile for combination therapy.

Conclusions: Combination therapy with mirabegron and tamsulosin is more effective than monotherapy in improving LUTS in patients with BPH, particularly storage symptoms, with a comparable safety profile. A fixed-dose combination formulation in the future may further improve patient adherence and quality of life.

Keywords: Lower urinary tract symptoms; Mirabegron; Prostatic hyperplasia; Tamsulosin; Urinary bladder, overactive

INTRODUCTION

Benign prostatic hyperplasia (BPH) prevalence increases with age, leading to a rising number of hospital visits [1,2]. It is a progressive disease that can cause benign prostatic enlargement and obstruction, resulting in Lower urinary tract symptoms (LUTS), which include storage (*e.g.*, frequency, urgency), voiding (*e.g.*, weak stream, hesitancy), and postmicturition symptoms (*e.g.*, incomplete emptying, dribbling) [3,4]. Overactive bladder (OAB) is also common in older adults, with BPH being a major cause due to bladder compression or neurological changes. Around 40% to 50% of BPH patients experience OAB symptoms, and even after BPH treatment, 38% may still have OAB. In cases of BPH accompanied by OAB, monotherapy with α-blockers alone has been found to be insufficient in achieving satisfactory treatment outcomes. Moreover, storage symptoms caused by OAB are known to cause greater distress to patients than voiding symptoms [5-7].

Alpha-blockers, which have been widely used as a first-line treatment for BPH, have demonstrated excellent symptom improvement. The selective alpha-blocker tamsulosin, through its specific mechanism of action, reduces the risk of adverse event and has been widely used to improve LUTS in BPH patients [8,9]. However, while alpha-blockers are effective in alleviating voiding symptoms, they have limitations in addressing storage symptoms.

Antimuscarinic agents, commonly used for OAB, affect both uninhibited and normal bladder contractions, potentially reducing detrusor contractility, increasing residual urine volume, and worsening bladder outlet obstruction (BOO), which may lead to acute urinary retention. Thus, caution is required. In contrast, mirabegron, a selective β3-adrenergic receptor agonist, acts during bladder relaxation without impairing normal contractions, minimizing the risk of residual urine increase or acute urinary retention. It also causes fewer side effects like dry mouth and dry eyes [10,11]. Notably, post void residual urine volume (PVR) changes showed no significant difference before and after mirabegron administration, with 150mL increases observed in 0.7% (placebo), 0.8% (tolterodine 4 mg), and 0% (mirabegron 50 mg) of patients [12,13].

BPH is a condition that significantly impacts patients' quality of life (QoL). Therefore, it is important to set treatment goals aimed at improving QoL and to decide on treatment methods from the patient's perspective. In particular, for BPH patients with LUTS, while improvement in voiding symptoms is important, it is even more critical to quickly alleviate and maintain relief from storage symptoms such as frequency and urgency, which are often more distressing [6,7].

To rapidly improve and sustain the alleviation of LUTS in BPH patients, continuous long-term pharmacotherapy is required. Furthermore, to prevent treatment discontinuation due to adverse events, QoL

deterioration, or insufficient therapeutic efficacy, the application of combination therapy as an initial therapy is considered necessary. Therefore, this study aimed to evaluate the efficacy and safety of mirabegron/tamsulosin combination therapy compared to tamsulosin monotherapy in BPH patients with LUTS.

MATERIALS AND METHODS

1. Study design and objectives

This study was a randomized, double-blind, parallel-group, placebo-controlled, multicenter phase 3 clinical trial conducted across 25 centers from July 2021 to October 2023. The trial evaluated the efficacy of mirabegron/tamsulosin combination therapy compared to tamsulosin monotherapy in men with LUTS. The study was approved by independent ethics committees and was conducted in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations.

If a participant was taking any medication that could affect LUTS, a wash-out period was implemented before the randomization visit, during which the participant stopped taking the medication. The duration of the wash-out period ranged from one to four weeks, contingent on the type and pharmacokinetic properties (*e.g.,* half-life) of the medication employed. Medications requiring a wash-out included α-blockers other than tamsulosin and 5α-reductase inhibitors, among others. Participants were required to discontinue these medications throughout the wash-out period and achieve symptom stability prior to randomization. Depending on whether a wash-out period was required, the screening period was shortened or extended. Participants maintained a voiding diary for three consecutive days prior to the randomization visit, and underwent tests including electrocardiogram (ECG), laboratory tests, digital rectal examination (DRE), transrectal ultrasonography (TRUS), International Prostate Symptom Scores (IPSS), uroflowmetry, and bladder scanning. Eligible participants who met the final inclusion/exclusion criteria were randomly assigned at each study site. They were allocated in a 1:1 ratio to either the mirabegron 50 mg/tamsulosin 0.4 mg combination therapy group (combination therapy group) or the tamsulosin 0.4 mg/placebo monotherapy group (monotherapy group), and received the study medication for 12 weeks. Participants visited the study site at weeks 4, 8, and 12 for assessments of efficacy and safety. At each visit, participants maintained a voiding diary and underwent IPSS, uroflowmetry, and bladder scanning. Additionally, all adverse events that occurred during the entire study period were collected, regardless of their relationship to the study drug.

2. Patients

During screening, participants were selected based on the inclusion and exclusion criteria. Eligible participants were males aged 40 or older with a BPH diagnosis confirmed by DRE or TRUS, an IPSS score of 13 or higher, and a voiding frequency of at least eight times per day, with urgency occurring at least twice daily (patient perception of intensity of urgency scale [PPIUS] grade ≥3) according to a three-day voiding diary. Uroflowmetry requirements included a voided volume of at least 120 mL and a maximum flow rate (Qmax) between 4 and 15 mL/sec, while PVR had to be under 200 mL.

Exclusion criteria included hypersensitivity to the trial drug, a history of pelvic malignancy within five years, prior or planned pelvic organ surgery, BOO requiring catheterization in the past 12 weeks, surgery affecting uroflowmetry, electrical stimulation therapy for OAB, other conditions causing LUTS, current or recurrent urinary tract infections, and a prostate-specific antigen level of 10.0 ng/mL or higher.

3. Efficacy assessments

The primary efficacy endpoint was the change in total urinary frequency score (TUFS) and the change in the total IPSS score at the 12-week post-treatment visit compared to baseline. TUFS was calculated based on the frequency of urination recorded in the voiding diary and the urgency score assessed using the PPIUS. The urgency score for each urination event was summed and then divided by the number of days the voiding diary was maintained to calculate the average daily TUFS [14,15].

The secondary efficacy endpoints included the change in the average daily frequency of daytime urination, nighttime urination, urgency episodes, incontinence episodes, and urge incontinence episodes at the 12-week post-treatment visit compared to baseline. Additionally, the changes in IPSS scores for voiding symptoms, storage symptoms, and QoL scores, as well as the changes in PVR and Qmax were evaluated.

4. Safety assessments

Safety variables included adverse events, PVR, Qmax, vital signs, ECG parameters, physical examination, and standard laboratory measurements.

5. Statistical methodology

Statistical analysis was performed using SAS Enterprise Guide (version 8.2 or higher), with version 9.4 64-bit (SAS Institute Inc.). The safety analysis was conducted using the safety set, the primary analysis for proving superiority was conducted using the full-analysis set (FAS), and the primary analysis for proving non-inferiority was conducted using the per-protocol set (PPS). The primary efficacy evaluation for TUFS was analyzed using analysis of covariance (ANCOVA) with baseline values as a covariate. The total IPSS score was also analyzed using ANCOVA with baseline values as a covariate, and the least squares mean difference with two-sided 95% confidence intervals (95% CIs) (one-sided 97.5% CI) was presented. The secondary efficacy evaluations were also analyzed using ANCOVA with baseline values as a covariate. For safety, treatment-emergent adverse events (TEAEs) were analyzed by reporting the number of participants, incidence rates, and occurrences by treatment group, and analyzed using Fisher's exact test.

6. Ethics statement

The present study protocol was reviewed and approved by the institutional review board of Gyeong-

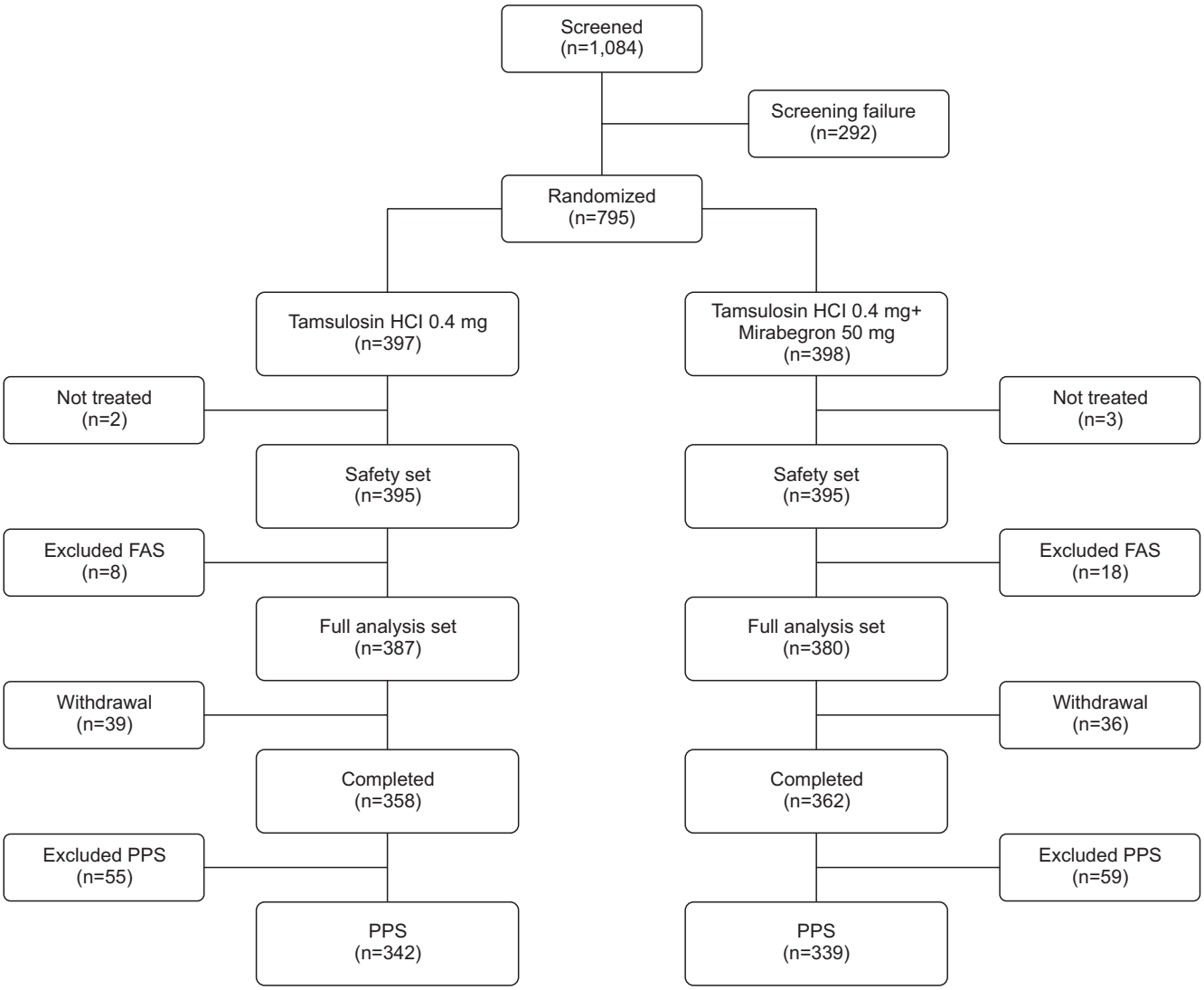

Fig. 1. Flowchart of study of randomized, double-blinded, parallel-group, placebo-controlled clinical research to validate the efficacy and safety of the combination of tamsulosin and mirabegron. FAS: full-analysis set; PPS: per-protocol set.

sang National University Changwon Hospital (Reg. No. 2021-05-008). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

A total of 1,084 participants were recruited, and 795 eligible participants were ultimately enrolled and randomly assigned to two groups: the monotherapy group (n=397) and the combination therapy group (n=398). In the monotherapy group, 2 participants did not receive treatment, 8 were excluded from the FAS due to protocol violations, withdrawal of consent prior to treatment, or loss to follow-up, 39 participants withdrew during the study, and 55 were excluded from the PPS due to major protocol deviations or missing primary endpoint data. In the combination therapy group, 3 participants did not receive treatment, 18 were excluded from the FAS, 36 withdrew during the study, and 59 were excluded from the PPS. In total, 342 participants in the monotherapy group and 339 participants in the combination therapy group completed the 12-week treatment (Fig. 1).

There were no statistically significant differences between the two groups in terms of age, weight, height, body mass index, duration of BPH, and duration of LUTS (Table 1).

1. Primary efficacy evaluation

The results from the FAS analysis showed that the change in TUFS from baseline to week 12 was -8.30±0.39 points in the monotherapy group and -11.28±0.39 points in the combination therapy group. The difference in scores between the combination therapy group and the monotherapy group was -2.98±0.55 points (95% CI: -4.06, -1.89), which was statistically significant (p<0.0001). The combination therapy group showed a greater reduction in TUFS scores compared to the monotherapy group, indicating an improvement in their condition and demonstrating the superiority of the combination therapy over the monotherapy. The PPS results were consistent with the FAS results.

The PPS analysis showed that the change in total IPSS score from baseline to week 12 was -9.85±0.33 points in the monotherapy group and -10.85±0.33 points in the combination therapy group. The difference in scores between the combination therapy group and the monotherapy group was -1.00±0.47 points (95% CI: -1.92, -0.08), which was statistically significant (p=0.0325). The combination therapy group showed a greater reduction in IPSS scores compared to the monotherapy group, confirming the improvement of their condition and demonstrating the non-inferiority of the combination therapy to the monotherapy. The PPS results were consistent with the FAS results (Table 2, Fig. 2).

2. Secondary efficacy evaluation

1) IPSS subscores

A significant improvement was observed in the combination therapy group compared to the monotherapy group in the IPSS storage subscore (p<0.001) and QoL score (p=0.0337). However, no statistically significant difference was found between the combination therapy group and the monotherapy group in the IPSS voiding subscore (p=0.4293) (Table 2).

Table 1. Demographics and baseline characteristics

	Tamsulosin+placebo (n=397)	Tamsulosin+mirabegron (n=398)	p-value
Age (y)	60.8±10.10	60.4±9.82	0.5532
Weight (kg)	72.11±9.75	71.82±10.43	0.6790
Height (cm)	169.51±5.90	169.6±6.03	0.8280
BMI (kg/m^2)	25.07±2.93	24.90±2.87	0.4159
Duration of BPH (y)	0.07±0.38	0.12±0.71	0.1985
Duration of LUTS (y)	3.35±3.82	3.60±4.70	0.3928
Hyperlipidemia	86 (21.66)	81 (20.35)	
HTN	154 (38.79)	141 (35.43)	
DM	83 (20.91)	64 (16.08)	

Values are presented as mean±standard deviation or number (%).
BMI: body mass index, BPH: benign prostatic hyperplasia, LUTS: lower urinary tract symptoms, HTN: hypertension, DM: diabetes mellitus.

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Table 2. Changes in efficacy variable from baseline at 12 week treatment period

	Tamsulosin+placebo	Tamsulosin+mirabegron	p-value
TUFS (FAS)			<0.0001
Number	387	380	
Baseline	21.26±7.90	21.01±7.17	
Change	-8.30 (0.39)	-11.28 (0.39)	
Treatment difference		-2.98 (0.55)	
Total IPSS (PPS)			0.0325
Number	342	339	
Baseline	21.1±5.41	21.3±5.41	
Change	-9.85 (0.33)	-10.85 (0.33)	
Treatment difference		-1.00 (0.47)	
Average of daytime urination per day (FAS)			<0.0001
Number	387	380	
Baseline	8.32±2.30	8.18±2.17	
Change	-1.08 (0.09)	-1.62 (0.09)	
Treatment difference		-5.04 (0.13)	
Average of night urination per day (FAS)			0.4734
Number	387	380	
Baseline	2.40±1.16	2.40±1.07	
Change	-1.08 (0.09)	-1.62 (0.09)	
Treatment difference		-5.04 (0.13)	
Average of urinary urgency per day (FAS)			<0.0001
Number	387	380	
Baseline	8.32±2.30	8.18±2.17	
Change	-0.60 (0.04)	-0.56 (0.04)	
Treatment difference		0.04 (0.06)	
Average of urinary incontinence per day (FAS)			0.0054
Number	387	380	
Baseline	0.71±1.81	0.60±1.40	
Change	-0.31 (0.05)	-0.51 (0.05)	
Treatment difference		-0.20 (0.07)	
Average of urge incontinence per day (FAS)			0.0027
Number	387	380	
Baseline	0.31±0.79	0.31±0.93	
Change	-0.15 (0.03)	-0.27 (0.03)	
Treatment difference		-0.12 (0.04)	
IPSS voiding symptom score (FAS)			0.4293
Number	387	380	
Baseline	11.9±4.12	12.2±4.11	
Change	-5.81 (0.20)	-6.03 (0.20)	
Treatment difference		-0.22 (0.28)	
IPSS storage symptom score (FAS)			0.0001
Number	387	380	
Baseline	9.1±2.36	9.0±2.48	
Change	-3.74 (0.14)	-4.51 (0.14)	
Treatment difference		-0.77 (0.20)	

Table 2. Continued

	Tamsulosin+placebo	Tamsulosin+mirabegron	p-value
PVR (FAS)			0.0337
Number	387	380	
Baseline	37.18±40.83	35.46±39.21	
Change	-11.11 (1.85)	-5.53 (1.86)	
Treatment difference		5.58 (2.62)	
Qmax (FAS)			0.6272
Number	387	380	
Baseline	10.61±2.75	10.70±2.93	
Change	5.39 (0.44)	5.08 (0.44)	
Treatment difference		-0.30 (0.63)	

Values are presented as mean±standard deviation or least squares mean (standard error).
TUFS: total urinary frequency score, FAS: full-analysis set, IPSS: International Prostate Symptom Scores, PPS: per-protocol set, PVR: post void residual volume, Qmax: maximum urinary flow rate.

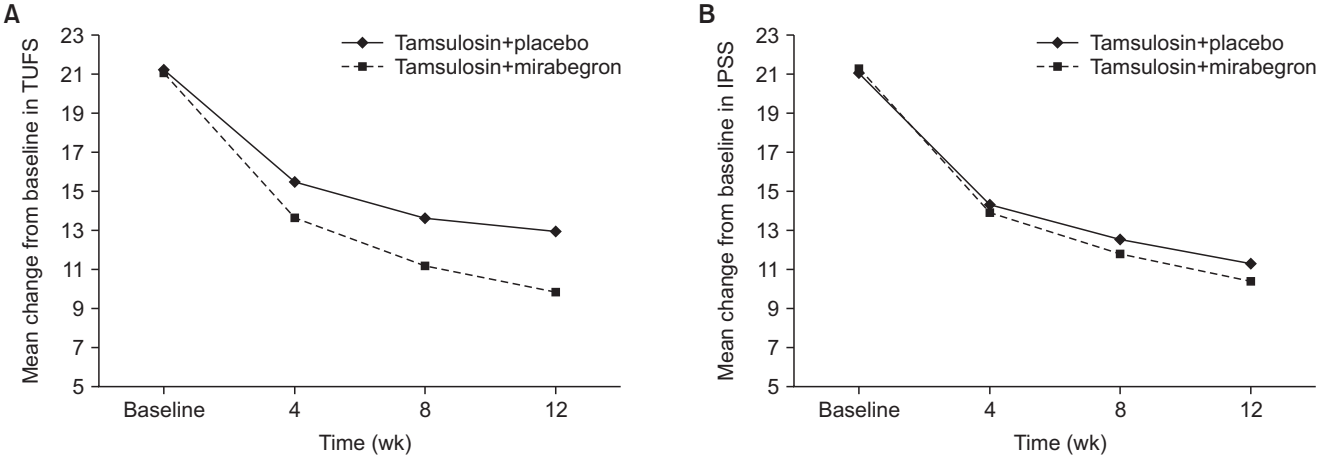

Fig. 2. Panels show mean changes from baseline in TUFS (A) and total IPSS (B), respectively, during the treatment periods. TUFS: total urinary frequency score, IPSS: International Prostate Symptom Scores.

2) Micturition diary variables

Compared to the monotherapy group, the combination therapy group showed statistically significant differences in the following voiding diary variables: daytime micturition frequency (p<0.0001), urgency frequency (p<0.0001), incontinence frequency (p=0.0038), urge incontinence frequency (p=0.0007), and change in PVR (p=0.0054). However, no statistically significant differences were found for nighttime micturition frequency (p=0.4734) and change in Qmax (p=0.7530) (Table 2).

3. Safety

During the clinical trial, the incidence of TEAEs after the administration of the clinical trial drug was 13.16% in the monotherapy group and 16.71% in the combination therapy group, with no statistically significant difference between the groups (p=0.1943). The most frequently reported common drug-related adverse events in the monotherapy group were 'dizziness' at 1.27%, followed by 'retrograde ejaculation' and 'ejaculation disorder' at 1.01%. In the combination therapy group, 'retrograde ejaculation' was the most common adverse event, occurring in 1.27% (Table 3).

When considering the overall occurrence of adverse events in the study participants, no specific or significant adverse events were identified in relation to tamsulosin or mirabegron, as expected based on known safety profiles. All serious adverse events were deemed to be related to external factors, with no association to tamsulosin or mirabegron. No abnormalities were found in laboratory tests, vital signs, physical exams, or

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Table 3. Summary of adverse events

	Tamsulosin+placebo (n=397)	Tamsulosin+mirabegron (n=398)
Any TEAEs	52 (13.1)	66 (16.58)
Serious AEs	2 (0.50)	4 (1.00)
ADR[a)]	33 (8.31)	31 (7.79)
Intensity		
Mild	28 (7.05)	31 (7.79)
Moderate	5 (1.26)	0 (0)
Severe	0 (0)	0 (0)
SADR	0 (0)	0 (0)
Common drug-related AEs		
Dizziness	5 (1.26)	3 (0.75)
Retrograde ejaculation	4 (1.00)	5 (1.25)
Ejaculation disorder	4 (1.00)	2 (0.50)

Values are presented as number (%).
TEAE: treatment-emergent adverse event, AE: adverse event, ADR: adverse drug reaction, SADR: serious adverse drug reaction.
[a)]ADR occuring in at least 1% of each analysis group.

electrocardiogram results. Therefore, the safety profile of the mirabegron/tamsulosin combination therapy in BPH patients with LUTS was confirmed to be acceptable when compared to tamsulosin monotherapy during the clinical trial period.

DISCUSSION

As the aging population increases, the incidence of OAB due to BPH is gaining attention, especially because of its significant impact on the QoL of elderly patients, particularly male patients. OAB is closely related to storage symptoms in BPH and LUTS. Mirabegron has shown superior efficacy with fewer side effects, proving to be more effective than antimuscarinics in the treatment of OAB. Studies have demonstrated that the combination of mirabegron and tamsulosin yields better results in treating patients with OAB and BPH compared to mirabegron alone [11,14,15]. Additionally, mirabegron combination therapy may improve the QoL in OAB patients [16].

The results of this study showed similar improvements to previous studies. These outcomes suggest that combining a β3-adrenergic receptor agonist and an alpha-blocker may have a synergistic effect in improving urinary symptoms, based on their distinct mechanisms of action. Beta-3 adrenergic receptor agonists induce relaxation of the bladder detrusor muscle, facilitating urination and alleviating OAB symptoms [17]. On the other hand, alpha-blockers relax the smooth muscles of the prostate and bladder neck, easing urination [3]. Therefore, using these two drugs together can address both OAB and LUTS simultaneously. Furthermore, greater improvements are expected with combination therapy compared to alpha-blocker monotherapy for LUTS.

Similar to the findings of other studies, this study demonstrated that the combination therapy of mirabegron/tamsulosin showed significant improvement in the IPSS storage subscore compared to tamsulosin monotherapy [18]. Positive effects were also observed in overall evaluations, including TUFS, IPSS total score, daytime urination frequency, urgency frequency, incontinence frequency, and urgency incontinence frequency. These improvements, coupled with improvements in QoL, highlight the significant clinical relevance of symptom alleviation for patients.

In the SATURN study, the TUFS change over 12 weeks was -4.76 points in the placebo group and -8.69 points in the experimental group, with a difference of -3.93 points [14]. Similarly, in the NEPTUNE study, the TUFS change was -6.70 points in the placebo group and -8.10 points in the experimental group, with a difference of -1.40 points [15]. In this trial, the TUFS change at 12 weeks was -8.30 in the monotherapy group and -11.28 in the combination group, showing a greater reduction in the combination therapy group compared to previous trials. The difference in mean change between the groups was -2.98, similar to the previously reported -2.67, confirming the trial's efficacy. The combination

therapy of tamsulosin and mirabegron significantly improved storage symptoms (urgency and frequency). The change in IPSS total score was -9.85 in the monotherapy group and -10.85 in the combination group, showing a better reduction trend compared to the SATURN and NEPTUNE studies [14,15].

Compared to the SATURN and NEPTUNE studies, which primarily evaluated the efficacy of solifenacin combined with tamsulosin in patients with OAB or LUTS/BPH, the present study focused on the combination of a β3-adrenergic receptor agonist (mirabegron) and tamsulosin. The β3-adrenergic receptor agonist is known not toaffect urinary contraction, thereby reducing the occurrence of urinary retention. This is related to the fact that mirabegron and tamsulosin have an antagonistic role in promoting urination. Other studies have shown that tamsulosin is used to reduce the risk of post-surgical urinary retention, as it relaxes the bladder neck and promotes urination, preventing urine volume/PVR accumulation. This suggests that mirabegron has a positive antagonistic effect in maintaining bladder contractility. In the present study, the change in PVR was -11.11±1.85 mL in the monotherapy group and -5.53±1.86 mL in the combination therapy group. The difference between the combination therapy and monotherapy groups was 5.58±2.62 mL, which showed a statistically significant difference (p=0.0337). This was similar to the findings observed in the MIRACLE study, which evaluated the efficacy of mirabegron in treating OAB [19]. Considering the literature reporting that a mean difference of approximately 10 mL in PVR is not clinically significant, this difference is not deemed to be clinically meaningful [20]. Moreover, no adverse events such as acute urinary retention were reported in either group.

During the clinical trial period, the incidence rate of TEAEs was 13.16% (52/395 subjects, 64 cases) in the monotherapy group and 16.71% (66/395 subjects, 87 cases) in the combination therapy group, with no statistically significant difference between the groups (p=0.1943). In the previously mentioned SATURN and NEPTUNE studies, the incidence rates of adverse events with tamsulosin monotherapy were 18.6% (33/177 subjects) and 22.7% (74/326 subjects), respectively, while the incidence rates with the combination of solifenacin 6 mg were 19.7% (35/178 subjects) and 29.4% (99/337 subjects), respectively [14,15]. Compared to these earlier studies, the present trial showed a relatively lower incidence of adverse events. This suggests that the safety profile of tamsulosin when combined with mirabegron does not significantly differ from that of tamsulosin monotherapy.

Importantly, this study highlights the potential benefits of a combination therapy in improving both efficacy and safety profiles for patients, especially in a population where managing symptoms effectively without significant side effects is crucial. The clinical significance of the findings lies in the fact that the combination of mirabegron and tamsulosin may serve as a key therapeutic strategy for managing LUTS in patients with BPH. This approach not only improves symptom control and QoL but also effectively reduces the risk of recurrent storage symptoms related to OAB, delays disease progression, and minimizes the need for further interventions. In terms of cost-effectiveness, although mirabegron is relatively more expensive than traditional medications, its superior tolerability and adherence may reduce treatment discontinuation and the associated healthcare costs, thereby improving the overall efficiency and cost-benefit ratio of therapy. Previous studies have shown that, in the field of urology, the combination of tamsulosin and dutasteride is more effective in improving male LUTS symptoms than either monotherapy alone [21], further supporting the feasibility and clinical value of developing a fixed-dose combination of mirabegron and tamsulosin in the future.

However, several limitations must be acknowledged. First, the follow-up period in this study was relatively short and may be insufficient to fully evaluate the long-term efficacy, patient adherence, and potential delayed adverse events associated with the combination therapy. Future studies with extended observation periods are needed to validate the durability and stability of the findings. Second, the participants in this study were primarily from Korea. Although the trial was conducted across multiple centers and the sample had a certain level of representativeness, there are still limitations related to ethnicity and geographic region. Therefore, the generalizability of the results to other countries or ethnic populations requires further investigation. In addition, this study employed an active comparator design using monotherapy and did not include a placebo group. While monotherapy is clinically relevant as a real-world comparator, the absence of a placebo group may limit the ability to distinguish

the true effect of the combination therapy, especially since notable improvements were also observed in the monotherapy group. Future studies may consider including a placebo arm to more clearly determine the drug's efficacy. Moreover, this study did not perform subgroup analyses based on different age groups or comorbidities such as diabetes and hypertension. Future research should consider stratified analyses to explore the actual effectiveness and applicability of combination therapy in diverse patient populations.

CONCLUSIONS

In conclusion, compared to tamsulosin monotherapy, combination therapy with mirabegron 50 mg and tamsulosin 0.4 mg significantly improves LUTS in patients with BPH, particularly storage symptoms, without increasing adverse events. This combination therapy represents a promising treatment option.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: Tae Hyo Kim, SCK. Data curation: All authors. Formal analysis: SCK, Tae Hyo Kim. Writing – original draft: SCK, YSS, Tae Hyo Kim. Writing – review & editing: SCK, Tae Hyo Kim.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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