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Original Article

An open-label, randomized, post-authorization study of mirabegron in Chinese participants with overactive bladder

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KEYWORDS
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Abstract *Objective:* To assess efficacy and safety of mirabegron 25 mg/day and 50 mg/day for overactive bladder in Chinese participants.
Methods: Participants of ≥18 years with overactive bladder symptoms lasting for ≥12 weeks, a mean of ≥8 micturitions per 24 h, and a mean of at least one episode of Grade 3 or 4 urgency or urge incontinence per 24 h based on the Patient Perception of Intensity of Urgency Scale over a 3-day micturition diary period were randomized 2:1 to open-label treatment with oral mirabegron 50 mg or 25 mg once daily for 12 weeks (15 sites in China, January 2021–March 2022). A dose escalation from 25 mg/day to 50 mg/day was permitted at weeks 4 and 8 according to the

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investigators' discretion. The primary efficacy endpoint was the change from baseline to Week 12 in the mean number of micturitions per 24 h in those randomized to mirabegron 50 mg/day. Secondary efficacy endpoints were the change in mean number of micturitions at weeks 4 and 8 in the mirabegron 50 mg/day group and weeks 4, 8, and 12 in the mirabegron 25 mg/day group, change from baseline to weeks 4, 8, and 12 in Grade 3 or 4 urgency episodes on the Patient Perception of Intensity of Urgency Scale, episodes of daytime incontinence, nighttime incontinence, and urgency incontinence, and Overactive Bladder Symptom Score for mirabegron 50 mg/day and 25 mg/day groups.

Results: Statistically significant reduction ($p<0.001$) from baseline to Week 12 was observed in mean micturitions per 24 h for participants randomized to mirabegron 50 mg/day: mean±standard error: 11.71±0.43 at baseline, 7.80±0.24 at Week 12; adjusted mean change: −3.73 (95% confidence interval −4.30 to −3.16). Both doses showed statistically significant improvement in secondary efficacy endpoints at weeks 4, 8, and 12 versus baseline. Safety was consistent with mirabegron's known safety profile.

Conclusion: The results support a mirabegron dosage of 50 mg/day for the treatment of OAB in China.

1. Introduction

Overactive bladder (OAB) is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, in the absence of proven infection or other obvious pathology that would explain these symptoms [1]. Previous studies have confirmed the substantial impact of OAB on daily activities and health-related quality of life [2,3]. Conservative approaches, including weight loss, smoking cessation, and bladder training, are recommended initial approaches to manage OAB [4]. Antimuscarinics have been the main pharmacotherapeutic approach for OAB over the past few decades if conservative strategies are ineffective [5]. However, they are associated with specific anticholinergic side effects, including dry mouth, constipation, and cognitive effects [6] and an increased risk of developing dementia [7], as well as the low adherence [8]. Therefore, the use of therapeutics that do not have these drawbacks could potentially improve patients' health-related quality of life.

Mirabegron, a first-in-class β_3-adrenoceptor agonist, is approved for the treatment of OAB in 62 countries globally and can be considered as an alternative to antimuscarinics in patients who fail conservative treatment [4,9]. The efficacy and safety of mirabegron have been proved in a number of phase 3 clinical trials [10—13], most of which involved Western or Japanese participants. Additional studies have shown that mirabegron appears to be as effective as antimuscarinics and is associated with a lower incidence of drug-related treatment-emergent adverse events (TEAEs) [14,15]; however, data from the China mainland is scarce. Due to the lack of data in the Chinese population, the China National Medical Products Administration requested further investigation into the use of mirabegron in Chinese participants. The current data were requested by the Chinese authority to fulfill the requirement for the mirabegron import drug license renewal in China. In Europe countries, Brazil, Japan, and other Asian countries and regions (including Hong Kong, China and Republic of Korea), the recommended dose is 50 mg/day, while a dose of 25 mg/day is reserved for special populations (*e.g.*, patients with severe renal impairment or moderate hepatic impairment) [16]. In North America, Australia, and some Asian countries (*e.g.*, Singapore and Malaysia), the recommended starting dose is 25 mg/day, with an optional increase to 50 mg/day [17].

The objectives of this study were to evaluate the efficacy of mirabegron 50 mg/day for treatment of OAB in Chinese participants, to explore the efficacy of mirabegron 25 mg/day, and to evaluate the safety of mirabegron over the 12 weeks of study. The study was a commitment to the regulatory authority who mandated local efficacy data on mirabegron in a Chinese population 5 years after its launch.

2. Participants and methods

2.1. Study design

This was an open-label, randomized, multicenter, 12-week, prospective, interventional, postauthorization study in Chinese participants with OAB treated with mirabegron (ClinicalTrials.gov Identifier: NCT04562090). The study was conducted from January 2021 to March 2022 at 15 sites in China (Beijing Hospital, Beijing [the lead agency of this study]; Lanzhou University Second Hospital, Lanzhou; Wuxi People's Hospital, Wuxi; General Hospital of Nuclear Industry, Soochow University, Suzhou; Beijing Friendship Hospital, Capital Medical University, Beijing; Henan Provincial People's Hospital, Zhengzhou; Guangzhou First People's Hospital, Guangzhou; West China Hospital, Sichuan University, Chengdu; Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan; The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an; Huashan Hospital, Fudan University, Shanghai; Beijing Chaoyang Hospital, Capital Medical University, Beijing; Sun Yat-sen Memorial

Hospital, Sun Yat-sen University, Guangzhou; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan; The First Hospital of Shanxi Medical University, Taiyuan), and it was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines. The study protocol was approved by the institutional review board for each site (the institutional review board approved No. of the lead agency of this study: 2020BJYYEC-153-02), and all participants provided written informed consent prior to performing any study-related procedures. Eligible participants had to be ≥18 years old and had to have exhibited symptoms of OAB for ≥12 weeks. They had to have a mean of eight or more micturitions per 24 h and a mean of at least one episode of Grade 3 or 4 urgency or urge incontinence per 24 h, based on scores according to the Patient Perception of Intensity of Urgency Scale (PPIUS) [18] during a 3-day micturition diary period. Full inclusion and exclusion criteria are shown in Supplementary Table 1.

Participants who met the screening-inclusion criteria were randomized in a 2:1 ratio to mirabegron 50 mg/day or 25 mg/day using a computer-generated randomization Interactive Web Response System to reduce the selection bias. This service was set up prior to the study to allow the real-time allocation of the treatment to the next eligible participant. Treatments were administered orally, once daily, at the same time after a meal during a 12-week, open-label treatment period. Study visits took place at weeks 4, 8, and 12, respectively. A follow-up visit took place within 14 days after the end of the treatment. For the mirabegron 25 mg/day group, a dose escalation to 50 mg/day was permitted at weeks 4 and 8 according to the investigator discretion.

2.2. Safety assessments

Safety was assessed throughout the study in terms of TEAEs, vital signs, 12-lead electrocardiograms, including QT interval corrected for heart rates by the Fridericia's formula, post-void residual volume, and laboratory evaluations.

2.3. Efficacy assessments

Only mirabegron 50 mg/day was assessed for the primary efficacy endpoint, which was the change from baseline to Week 12 in mean number of micturitions per 24 h in participants who were randomized to receive mirabegron 50 mg/day. Secondary efficacy endpoints consisted of the 25 mg/day dose. These were changes in the mean number of micturitions at weeks 4 and 8 in the mirabegron 50 mg/day group and at weeks 4, 8, and 12 in the mirabegron 25 mg/day group, and the change from baseline to weeks 4, 8, and 12 in Grade 3 or 4 urgency episodes on the PPIUS, daytime incontinence episodes, nighttime incontinence episodes, urgency urinary incontinence episodes, and scores according to the Overactive Bladder Symptom Score (OABSS) [19,20] in the mirabegron 50 mg/day and 25 mg/day groups. Data on micturition frequency and incontinence episodes were gathered via an e-diary, completed by participants at baseline and reviewed to check that they understood how to complete the diary, and then completed over 3 consecutive days in the week prior to weeks 4, 8, and 12, respectively.

2.4. Statistical analyses

The sample size was based on the change from baseline for the mean number of micturitions per 24 h within a single treatment arm. The change from baseline was tested to determine if the change was different from zero (*i.e.*, a change in the mean number of micturitions per 24 h). For a sample size of 125, a single group *t*-test with a 5% two-sided significance level would have 80% power to detect a change of 0.9 micturitions with a standard deviation (SD) of 3.562 [21]. Assuming 25% of the participants would drop out, about 166 participants would be enrolled to yield 125 evaluable participants in the mirabegron 50 mg/day group.

Efficacy data were evaluated using the full analysis set (FAS); participants had to receive at least one dose of the study drug and have at least one post-baseline measurement for the mean number of micturitions per 24 h. Safety data were evaluated using the safety analysis set (SAF), which consisted of data from participants who received at least one dose of the study drug. For the safety analysis, the mirabegron 50 mg/day group consisted of data from participants randomized to 50 mg/day and those randomized to 25 mg/day whose dose was up titrated to 50 mg/day; whereas the 25 mg/day group consisted of data from participants randomized to 25 mg/day while they were treated with 25 mg/day.

Continuous data were summarized descriptively, including the number of participants (*n*), mean, standard error of the mean (SEM), SD, median, minimum, and maximum. Categorical data were summarized by frequencies and percentages of participants, and descriptive statistics were used to analyze continuous variables.

The primary efficacy endpoint was analyzed using the mixed models for repeated measures (MMRM) model, including the visit (the repeated term), treatment group (25 mg/day [total] or 50 mg/day [as randomized]), pooled site, sex, interaction between the treatment group and visit as fixed effects, and baseline measurement (the mean number of micturitions per 24 h) as covariate. MMRM results were presented by treatment least squares (LS) mean (SEM) along with the two-sided 95% confidence interval (CI) and associated *p*-value for mean changes from baseline to weeks 4, 8, and 12. Data from participants who switched from mirabegron 25 mg to 50 mg daily were not included in the MMRM model after up titrating but were included up to the point of up titrating (*i.e.*, they were included only while receiving 25 mg/day).

All statistical comparisons were conducted using two-sided tests at the 5% significance level unless stated otherwise. All data summarization and analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA) on Linux.

2.5. Data-sharing statement

Researchers may request access to anonymized participant-level data, trial-level data, and protocols from

Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com; the Astellas criteria on data sharing could be found at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

3. Results

3.1. Study population

A total of 364 participants were screened, of which 115 (31.6%) were discontinued before randomization, resulting in 249 (68.4%) randomized (Fig. 1). Of the 249 participants randomized, one discontinued before receiving any treatment and was excluded from the SAF; 248 were included in the SAF and 241 in the FAS, and the latter consisted of 81 patients treated with mirabegron 25 mg/day and 160 patients with mirabegron 50 mg/day. The majority of participants were of Han ethnicity. For the FAS, the mean age in the mirabegron 50 mg/day group was 51.0 (SD 14.6) years; most (115/160, 71.9%) were female and had no prior OAB treatment (143/160, 89.4%) (Table 1). For those randomized to receive mirabegron 25 mg/day, the mean age was 47.7 (SD 15.5) years, most (62/81, 76.5%) were female, and had no prior OAB treatment (63/81, 77.8%). In total, 39 out of 83 (47.0%) participants on 25 mg/day were up titrated to 50 mg/day at some point during the study, with 35 out of 81 participants up titrated at Week 4, and four out of 45 (one withdrew after Week 4) participants up titrated at Week 8. Overall, demographic characteristics were similar between treatment groups (Table 1).

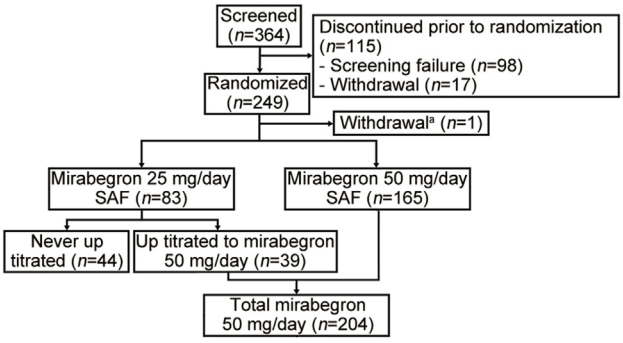

Figure 1 Participant disposition. For the SAF, the mirabegron 50 mg/day total group consisted of data from participants randomized to 50 mg/day and those randomized to 25 mg/day whose dose was up titrated to 50 mg/day; and the 25 mg/day group consisted of data from participants randomized to 25 mg/day. SAF, safety analysis set. [a] One participant did not take any dose of medication and withdrew from the trial.

3.2. Efficacy

For the primary endpoint, the mean number of micturitions at baseline was 11.71 (SEM 0.43) for participants randomized to 50 mg/day. At Week 12, there was a statistically significant decrease versus baseline: the adjusted LS mean change from baseline to Week 12 based on the MMRM was −3.73 (95% CI −4.30 to −3.16, $p<0.001$) (Table 2). There was a reduction in the mean number of micturitions per 24 h over time (Fig. 2).

For the secondary endpoints, mirabegron showed a statistically significant improvement (all $p<0.001$) in the mean number of micturitions per 24 h at weeks 4 and 8 in the mirabegron 50 mg/day group, and at weeks 4, 8, and 12 in the mirabegron 25 mg/day group. For the mirabegron 50 mg/day group, the adjusted LS mean changes (95% CI) from baseline were −2.36 (−2.90 to −1.81) to Week 4 and −2.92 (−3.47 to −2.37) to Week 8. For mirabegron 25 mg/day group, the adjusted LS mean changes (95% CI) from baseline were −1.97 (−2.73 to −0.21) to Week 4, −3.20 (−4.20 to −2.20) to Week 8, and −3.89 (−4.98 to −2.80) to Week 12.

For the secondary efficacy endpoint of the mean number of Grade 3 or 4 (PPIUS) urgency episodes per 24 h, mirabegron 50 mg/day and 25 mg/day showed a statistically

Table 1 Participant demographics and baseline characteristics by the FAS.

Variable	Mirabegron 25 mg/day (total) ($n=81$)	Mirabegron 50 mg/day (as randomized) ($n=160$)	Total mirabegron ($n=241$)
Sex, *n* (%)			
Male	19 (23.5)	45 (28.1)	64 (26.6)
Female	62 (76.5)	115 (71.9)	177 (73.4)
Age, year, mean (SD; range)	47.7 (15.5; 18–75)	51.0 (14.6; 18–83)	49.9 (14.9; 18–83)
Ethnicity, *n* (%)			
Achang	0	1 (0.6)	1 (0.4)
Dongxiang	0	1 (0.6)	1 (0.4)
Han	80 (98.8)	157 (98.1)	237 (98.3)
Hui	0	1 (0.6)	1 (0.4)
Lisu	1 (1.2)	0	1 (0.4)
Prior OAB treatment, *n* (%)			
Yes	18 (22.2)	17 (10.6)	35 (14.5)
No	63 (77.8)	143 (89.4)	206 (85.5)

FAS, full analysis set; OAB, overactive bladder; SD, standard deviation.
Note: data are shown for the FAS (participants who received at least one dose of the study drug and provided data for at least one variable before and after the start of the treatment period); percentages may not sum up to 100% due to rounding.

Table 2 The mixed models for repeated measures analysis of the mean number of micturitions per 24 h after mirabegron 50 mg/day treatment at Week 12.

Variable	Value
Baseline	
Patient, *n*	160
Micturitions per 24 h, mean (SEM)	11.71 (0.43)
Week 12	
Patient, *n*	147
Micturitions per 24 h, mean (SEM)	7.80 (0.24)
Change from baseline	
Patient, *n*	147
Micturitions per 24 h, mean (SEM)	−3.76 (0.40)
Adjusted change of the number of micturitions per 24 h[a]	
LS mean (SEM)	−3.73 (0.29)
95% CI	−4.30 to −3.16
p-Value	<0.001

LS, least squares; SEM, standard error of the mean; CI, confidence interval.
Note: data are shown for the full analysis set (participants who received at least one dose of the study drug and provided data for at least one variable before and after the start of the treatment period).
[a] The mixed models for repeated measures analysis was performed with the change from baseline to different visit time (weeks 4, 8, and 12) as response, treatment group, visit time (weeks 4, 8, and 12), pooled site, sex, the interaction between treatment group and visit as fixed effects, and mean number of micturitions per 24 h at baseline as covariate. The statistical testing was two-sided at a significance level of 0.05.

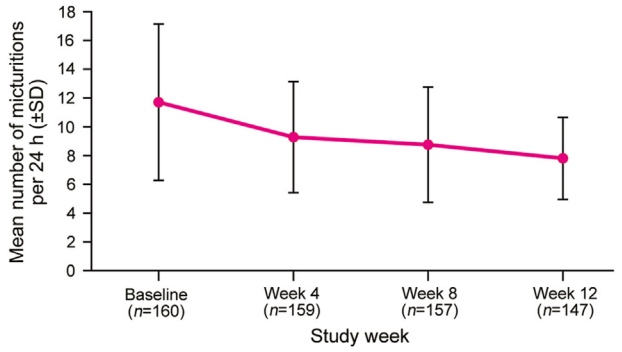

Figure 2 The full analysis set analysis for the number of micturitions per 24 h by study weeks for the mirabegron 50 mg/day treatment (as randomized). SD, standard deviation.

significant improvement (all $p<0.001$) at weeks 4, 8, and 12 versus baseline. For the mirabegron 50 mg/day group, the adjusted LS mean changes (95% CI) from baseline to weeks 4, 8, and 12 based on the MMRM were −2.47 (−2.93 to −2.02), −2.93 (−3.39 to −2.47), and −3.59 (−4.06 to −3.12), respectively. In the mirabegron 25 mg/day group, the adjusted LS mean changes (95% CI) from baseline to weeks 4, 8, and 12 based on the MMRM analysis were −2.62 (−3.25 to −1.99), −3.13 (−3.96 to −2.30), and −3.47 (−4.37 to −2.56), respectively (Supplementary Table 2).

For the secondary efficacy endpoint of the mean number of daytime incontinence episodes per 24 h, both doses of mirabegron showed statistically significant improvement (all $p<0.001$) at weeks 4, 8, and 12 versus baseline. For the mirabegron 50 mg/day group, the adjusted LS mean changes (95% CI) from baseline at weeks 4, 8, and 12 were −0.81 (−0.97 to −0.65), −0.94 (−1.10 to −0.78), and −0.98 (−1.14 to −0.81), respectively. For the mirabegron 25 mg/day group, the adjusted LS mean changes (95% CI) from baseline at weeks 4, 8, and 12 were −0.66 (−0.88 to −0.44), −0.88 (−1.17 to −0.58), and −1.03 (−1.35 to −0.71), respectively (Supplementary Table 3).

For all other secondary efficacy endpoints, both doses of mirabegron also showed statistically significant improvement (all $p<0.001$) at weeks 4, 8, and 12 versus baseline. For the mean number of nighttime incontinence episodes per 24 h, the adjusted LS mean changes (95% CI) from baseline to weeks 4, 8, and 12 were −0.46 (−0.53 to −0.38), −0.45 (−0.52 to −0.37), and −0.52 (−0.60 to −0.45), respectively, for the mirabegron 50 mg/day group; and −0.48 (−0.58 to −0.37), −0.53 (−0.67 to −0.39), and −0.53 (−0.68 to −0.38), respectively, for the mirabegron 25 mg/day group (Supplementary Table 4). For the mean number of urgency urinary incontinence episodes per 24 h, the adjusted LS mean changes (95% CI) from baseline to weeks 4, 8, and 12 were −1.11 (−1.25 to −0.96), −1.20 (−1.34 to −1.05), and −1.27 (−1.42 to −1.12), respectively, for the mirabegron 50 mg/day group; and −1.10 (−1.31 to −0.90), −1.26 (−1.53 to −0.99), and −1.25 (−1.54 to −0.96), respectively, for the mirabegron 25 mg/day group (Supplementary Table 5). The adjusted LS mean changes (95% CI) in OABSS from baseline to weeks 4, 8, and 12 were −3.05 (−3.44 to −2.65), −4.30 (−4.70 to −3.90), and −5.40 (−5.82 to −4.98), respectively, for the mirabegron 50 mg/day group; and −2.97 (−3.50 to −2.43), −5.09 (−5.80 to −4.39), and −6.01 (−6.78 to −5.24), respectively, for the mirabegron 25 mg/day group (Supplementary Table 6).

3.3. Safety

TEAEs occurred in 88/248 (35.5%) participants receiving total mirabegron (data from mirabegron 25 mg/day and 50 mg/day combined), with drug-related TEAEs occurring in 19/248 (7.7%) participants (Table 3). The most commonly reported drug-related TEAEs (≥1% of participants) were nausea, increased aspartate aminotransferase, and hypertension, which were reported by 3/248 (1.2%) participants each. In total, 14/248 (5.6%) participants treated with mirabegron experienced serious TEAEs. Of these, two were drug-related serious TEAEs: there was one case of moderate abnormal electrocardiogram ST segment and severe chest discomfort, which resolved on treatment discontinuation, and the other case was hypertension (moderate), which was not resolved during treatment. TEAEs reported in ≥2.0% of participants receiving total mirabegron by the preferred term were urinary tract infection in 10/248 (4.0%) participants and upper respiratory tract infection in 5/248 (2.0%) participants.

TEAEs of lower abdominal pain, gastrointestinal disorder, hypersensitivity, abnormal electrocardiogram ST segment, hypoesthesia, and bladder discomfort that led to the withdrawal of treatment were reported in 5 (2.0%)

Table 3 TEAEs occurring during the study.

TEAE	Mirabegron 25 mg/day (total) ($n=83$)	Mirabegron 50 mg/day (total) ($n=204$)	Total mirabegron ($n=248$)
Drug-related	3 (3.6)/4	16 (7.8)/31	19 (7.7)/35
Serious	4 (4.8)/4	10 (4.9)/13	14 (5.6)/17
Serious drug-related TEAE	1 (1.2)/1	1 (0.5)/2	2 (0.8)/3
Leading to withdrawal of treatment	1 (1.2)/1	4 (2.0)/5	5 (2.0)/6
Leading to death	0	0	0
Reported by $\geq$2.0% in any group			
Urinary tract infection	1 (1.2)/1	9 (4.4)/9	10 (4.0)/10
Upper respiratory tract infection	1 (1.2)/2	4 (2.0)/5	5 (2.0)/7
Protein urine present	2 (2.4)/2	0	2 (0.8)/2
Dizziness	2 (2.4)/2	2 (1.0)/2	4 (1.6)/4
Aspartate aminotransferase increased	0	4 (2.0)/4	4 (1.6)/4

TEAE, treatment-emergent adverse event.
Note: the data are shown for the safety analysis set (participants who received at least one dose of the study drug and provided data for at least one variable before and after the start of the treatment period); the mirabegron 50 mg/day total group consisted of data from participants randomized to 50 mg/day and those randomized to 25 mg/day whose dose was up titrated to 50 mg/day, whereas the 25 mg/day group included data from participants randomized to 25 mg/day; data are presented as the number of participants (%)/number of events.

participants. None of the TEAEs leading to withdrawal were reported in more than one participant; all these TEAEs were resolved. No new clinically meaningful safety findings were observed for laboratory parameters or other safety observations.

Although some participants had raised liver function test variables reporting as mild or moderate TEAEs, none had laboratory values that met the potentially clinically significant criteria for hepatotoxicity or total bilirubin or that required further liver function investigation.

4. Discussion

This was an open-label, randomized, prospective, interventional, postauthorization study to determine the efficacy and safety of mirabegron for the treatment of OAB in Chinese participants. The study was not designed to compare the 50 mg dose of mirabegron with the 25 mg dose daily. The primary outcome was the change from baseline to Week 12 in the mean number of micturitions per 24 h in participants who were randomized to receive mirabegron 50 mg/day. Product labelling differs between countries, with a recommended starting dose of 25 mg once daily in the US and Canada, with an option to increase to 50 mg/day, and a recommended dose of 50 mg once daily in Japan, European countries, Brazil, and other Asian countries and regions (including Hong Kong, China and Republic of Korea), with the 25 mg/day dose reserved for special populations (*e.g.*, those with severe renal impairment or moderate hepatic impairment).

In total, 47% of participants taking mirabegron 25 mg/day were up titrated to 50 mg/day at some point during the study, reflecting the superior efficacy of the 50 mg/day dose. This supports data from Herschorn et al. [22], which showed that although both doses of mirabegron demonstrated statistically significant improvements in the mean number of incontinence episodes and micturitions per 24 h compared with placebo, mirabegron 50 mg/day also demonstrated significantly greater improvements versus placebo in the mean volume voided per micturition (change from baseline to final visit) and the mean number of incontinence episodes per 24 h (change from baseline to Week 4).

In the current study, a statistically significant reduction ($p<0.001$) from baseline to Week 12 was observed in the primary efficacy endpoint: the mean number of micturitions per 24 h with mirabegron 50 mg/day. Both doses of mirabegron showed a statistically significant improvement in all secondary efficacy endpoints at weeks 4, 8, and 12 versus baseline. The results support a dosage of 50 mg/day as the recommended dose in China, except for those with hepatic or renal impairment.

In an analysis of pooled data from a 12-week, multinational, randomized, double-blind, parallel-group, placebo- and active-controlled trial in participants with symptoms of OAB in China, Republic of Korea, and India, mirabegron 50 mg once daily for 12 weeks was superior to placebo in reducing the mean number of micturitions per 24 h, with a statistically significant improvement with mirabegron 50 mg/day at all timepoints ($p<0.05$) as well as at Week 12 (final visit) (-0.57; 95% CI -1.04 to -0.09, $p=0.019$) [21]. Mirabegron was well tolerated overall, and no clinically relevant safety concerns were identified. A review of randomized controlled phase 3 trials of mirabegron conducted in Europe, Australia, and North America concluded that mirabegron at daily doses of 25 mg, 50 mg, and 100 mg demonstrated significant efficacy in treating symptoms of OAB, and doses of 50 mg/day and 100 mg/day demonstrated significant improvement compared with placebo on key secondary endpoints as early as the first assessment (Week 4), and the improvement was maintained throughout treatment [13]. In OAB clinical trials of $\leq$12 months, mirabegron appeared to be well tolerated [13]. Furthermore, a review of participants who had poor tolerability to antimuscarinics, or were elderly or male, found that mirabegron at doses of 25 mg per day and 50 mg per day was associated with clinically meaningful benefits according to patient-reported outcomes [23]. A favorable safety and tolerability profile of mirabegron was also reported, particularly compared with antimuscarinics, for dry

mouth, constipation, and many central nervous system effects, which was maintained over 12 months [23]. Additionally, the analysis of a large integrated database utilizing mirabegron studies from across the world and providing good representation of men and women of all ages reaffirmed the safety and efficacy profiles of mirabegron [24].

Safety in the current study was consistent with the known safety profile for mirabegron [24]. The most common TEAEs were infections and infestations, gastrointestinal disorders, and investigations; most were mild. The most commonly reported TEAEs in participants receiving total mirabegron were urinary tract infections and upper respiratory tract infections. Serious TEAEs were reported in 14 (5.6%) participants. Of these participants, two reported drug-related serious TEAEs. Overall, there appeared to be no new safety concerns with mirabegron over 12 weeks, and it was well tolerated in the Chinese population studied. There were no new clinically meaningful safety findings for laboratory parameters or other safety observations.

A limitation of the study is that the 50 mg/day and 25 mg/day doses of mirabegron were not directly compared. A further limitation is that there is no Chinese translation and validation of the PPIUS. Strengths of the study include the use of the OABSS, which evaluates subjective symptoms, with a higher OABSS indicating worse symptoms, and which was originally developed by the Japan Red Cross Medical Center to assess bother due to OAB symptoms (daytime frequency, nighttime frequency, urgency, and urge incontinence) during the past week [25]. It was translated into Chinese by the Chinese Urological Association and was found to have a good test—retest reliability and high correlation with other OAB rating tools (such as the International Prostate Symptom Score total score and the Patient Perception of Bladder Control) among Chinese patient with OAB [26]. The statistically significant improvement in OABSS was seen in the current study and has also been seen in a number of other mirabegron studies in Japan, including real-world studies [27—29].

5. Conclusion

Mirabegron was efficacious and well tolerated over the 12-week study. The results support a dosage of 50 mg/day as the recommended dose in the Chinese population.

Author contributions

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Conflicts of interest

Yingfan Yang (Medical Affairs, Astellas Pharma [China], Inc., Shenyang, China), Farid Abdul Hadi (Medical Affairs, Astellas Pharma Singapore Pte. Ltd., Singapore), and Arianne Schild (Analytics & Data Science, Astellas Pharma Global Development, Inc., Northbrook, IL, USA) are employees of Astellas. This study was funded by Astellas Pharma (China), Inc., Shenyang, China, and medical writing support was provided by Sue Cooper of Envision Pharma Ltd. (Horsham, UK). The authors declare no other conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2024.04.007.

References

[1] Drake MJ. Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. Neurourol Urodyn 2014;33:622—4.
[2] Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 2008;101:1388—95.
[3] Dmochowski RR, Newman DK. Impact of overactive bladder on women in the United States: results of a national survey. Curr Med Res Opin 2007;23:65—76.
[4] Harding CK, Lapitan MC, Arlandis S, Bø K, Cobussen-Boekhorst H, Costantini E, et al. EAU guidelines on management of non-neurogenic female lower urinary tract symptoms. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Non-neurogenic-Female-LUTS-2022_2022-05-12-115954_kvpr.pdf. [Accessed 3 July 2024].
[5] Athanasopoulos A, Giannitsas K. An overview of the clinical use of antimuscarinics in the treatment of overactive bladder. Adv Urol 2011;2011:820816. https://doi.org/10.1155/2011/820816.
[6] Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol 2008;54:543—62.
[7] Dmochowski RR, Thai S, Iglay K, Enemchukwu E, Tee S, Varano S, et al. Increased risk of incident dementia following use of anticholinergic agents: a systematic literature review and meta-analysis. Neurourol Urodyn 2021;40:28—37.
[8] Duperrouzel C, Martin C, Mendell A, Bourque M, Carrera A, Mack A, et al. Healthcare and economic burden of anticholinergic use in adults with overactive bladder: a systematic literature review. J Comp Eff Res 2022;11:1375—94.
[9] Nambiar AK, Arlandis S, Bo K, Cobussen-Boekhorst H, Costantini E, de Heide M, et al. European Association of Urology guidelines on the diagnosis and management of female non-neurogenic lower urinary tract symptoms. Part 1:

diagnostics, overactive bladder, stress urinary incontinence, and mixed urinary incontinence. Eur Urol 2022;82:49—59.
[10] Khullar V, Amarenco G, Angulo JC, Cambronero J, Hoye K, Milsom I, et al. Efficacy and tolerability of mirabegron, a β3-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European—Australian phase 3 trial. Eur Urol 2013;63:283—95.
[11] Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol 2013;189:1388—95.
[12] Yamaguchi O, Marui E, Kakizaki H, Homma Y, Igawa Y, Takeda M, et al. Phase III, randomised, double-blind, placebo-controlled study of the β_3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. BJU Int 2014;113:951—60.
[13] Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC. Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. Neurourol Urodyn 2014;33:17—30.
[14] Otsuka A, Kageyama S, Suzuki T, Matsumoto R, Nagae H, Kitagawa M, et al. Comparison of mirabegron and imidafenacin for efficacy and safety in Japanese female patients with overactive bladder: a randomized controlled trial (COMFORT study). Int J Urol 2016;23:1016—23.
[15] Torimoto K, Matsushita C, Yamada A, Goto D, Matsumoto Y, Hosokawa Y, et al. Clinical efficacy and safety of mirabegron and imidafenacin in women with overactive bladder: a randomized crossover study (the MICRO study). Neurourol Urodyn 2017;36:1097—103.
[16] Astellas Pharma Europe B.V. Betmiga. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/betmiga-epar-product-information_en.pdf. [Accessed 3 July 2024].
[17] Astellas Pharma US Inc. MYRBETRIQ. Prescribing information. Astellas; 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202611s011lbl.pdf. [Accessed 3 July 2024].
[18] Cartwright R, Srikrishna S, Cardozo L, Robinson D. Validity and reliability of the patient's perception of intensity of urgency scale in overactive bladder. BJU Int 2011;107:1612—7.
[19] Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, et al. Symptom assessment tool for overactive bladder syndrome-overactive bladder symptom score. Urology 2006;68:318—23.
[20] Chou EC, Hung MJ, Yen TW, Chuang YC, Meng E, Huang ST, et al. The translation and validation of Chinese overactive bladder symptom score for assessing overactive bladder syndrome and response to solifenacin treatment. J Formos Med Assoc 2014;113:506—12.
[21] Kuo HC, Lee KS, Na Y, Sood R, Nakaji S, Kubota Y, et al. Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a β_3-adrenoceptor agonist, in patients with overactive bladder in Asia. Neurourol Urodyn 2015;34:685—92.
[22] Herschorn S, Barkin J, Castro-Diaz D, Frankel JM, Espuna-Pons M, Gousse AE, et al. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology 2013;82:313—20.
[23] Chapple CR, Siddiqui E. Mirabegron for the treatment of overactive bladder: a review of efficacy, safety and tolerability with a focus on male, elderly and antimuscarinic poor-responder populations, and patients with OAB in Asia. Expet Rev Clin Pharmacol 2017;10:131—51.
[24] Chapple CR, Cruz F, Cardozo L, Staskin D, Herschorn S, Choudhury N, et al. Safety and efficacy of mirabegron: analysis of a large integrated clinical trial database of patients with overactive bladder receiving mirabegron, antimuscarinics, or placebo. Eur Urol 2020;77:119—28.
[25] Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, et al. Symptom assessment tool for overactive bladder syndrome—overactive bladder symptom score. Urology 2006;68:318—23.
[26] Wang Y, Xu K, Hu H, Zhang X, Wang X, Na Y, et al. Prevalence, risk factors, and impact on health related quality of life of overactive bladder in China. Neurourol Urodyn 2011;30:1448—55.
[27] Nozawa Y, Kato D, Tabuchi H, Kuroishi K. Safety and effectiveness of mirabegron in patients with overactive bladder in a real-world clinical setting: a Japanese post-marketing study. Low Urin Tract Symptoms 2018;10:122—30.
[28] Matsukawa Y, Takai S, Funahashi Y, Yamamoto T, Gotoh M. Urodynamic evaluation of the efficacy of mirabegron on storage and voiding functions in women with overactive bladder. Urology 2015;85:786—90.
[29] Otsuki H, Kosaka T, Nakamura K, Mishima J, Kuwahara Y, Tsukamoto T. β3-adrenoceptor agonist mirabegron is effective for overactive bladder that is unresponsive to antimuscarinic treatment or is related to benign prostatic hyperplasia in men. Int Urol Nephrol 2013;45:53—60.