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Cardiovascular safety of vibegron, a new β3-adrenoceptor agonist, in older patients with overactive bladder: Post-hoc analysis of a randomized, placebo-controlled, double-blind comparative phase 3 study

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Abstract

Aims: To examine the safety and efficacy of vibegron, a new β3-adrenoceptor agonist, in patients aged ≥65 years, with a focus on the effects on cardiovascular system and overactive bladder (OAB) symptoms.

Methods: A post-hoc subgroup analysis was performed of a randomized, placebo-controlled, double-blind comparative phase 3 study of vibegron, including those assigned to receive either vibegron 50 mg (V50), vibegron 100 mg (V100), or placebo for 12 weeks. Subjects were stratified into two subgroups based on age: a <65-year subgroup and a ≥65-year subgroup. Safety (changes in systolic and diastolic blood pressure, pulse rate, and residual urine volume) and efficacy (changes in the numbers of micturitions, urgency episodes, urgency urinary incontinence [UUI] episodes, and the voided volume/micturition) were assessed in the subgroups treated with vibegron vs. placebo.

Results: There were no significant differences in the cardiovascular outcomes (blood pressure and pulse rate), nor in the changes in residual urine volume, between the V50/100 and placebo groups in the <65-year or ≥65-year subgroup after 12-week treatment. Adverse events were slightly increased in the ≥65-year subgroup. In the efficacy analysis, V50/100 demonstrated similar efficacy in the <65-year and ≥65-year subgroups; an increasing trend in the voided volume/micturition was observed in subjects aged ≥65 years compared to subjects aged <65 years.

Conclusions: Vibegron was suggested to be similarly effective in patients ≥65 and <65 years and to have minimal influence on cardiovascular parameters.

KEYWORDS
aging, pharmacological therapy, subgroup, urinary symptom, urinary urgency

1 | INTRODUCTION

Overactive bladder syndrome (OAB) is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence (UUI).[1,2] The prevalence of OAB increases with age in both men and women.[3]

Although OAB is rarely life-threatening, it has a significant impact on quality of life as well as healthy life expectancy, and is an important issue in an aging society. Generally, multimorbidity and multimedication use are more likely to occur with aging; OAB patients may be suffering from several lifestyle-related diseases.

On the other hand, there are data challenging the idea that OAB is a normal part of aging. A 1-year follow-up survey performed in the UK that included over 19,000 women aged over 40 years concluded that OAB was independently predicted by poor health, and the association with older age disappeared after adjusting for several specific comorbidities.[4] Another study, performed in over 1300 patients aged ≥65 years, found that frailty was a statistically significant predictor of OAB, when adjusted for age, race, and sex.[5] These studies suggest that the condition is age-related rather than age-dependent. Although urological changes due to aging (such as bladder outlet obstruction associated with benign prostatic hyperplasia in men and weakening of the pelvic floor muscles in women) are known causes of OAB, the functional changes associated with aging vary greatly among individuals. Therefore, normal bladder function can be set as a goal through optimal treatment, even in older populations.

OAB treatment includes lifestyle modification, such as avoiding excessive fluid intake, behavioral therapy, such as pelvic floor muscle training and bladder training to gradually prolong the interval between micturitions, and pharmacological therapy aimed at suppressing involuntary bladder contractions and/or inhibiting the activity of bladder afferent nerves conveying bladder sensation.[6,7]

Related to the pathophysiology of OAB, three β-AR subtypes (β1, β2, and β3) have been identified in the bladder detrusor muscle and urothelium.[8,9] Among them, β3-AR is dominant in the human bladder accounting for 97% of total β-ARs,[10,11] which is thought to be the main subtype mediating relaxation of detrusor smooth muscle during the storage phase.[12] These three β-ARs are also expressed in the cardiovascular system and compounds with relatively limited β3-AR agonist selectivity and activity reportedly trigger positive inotropic effects in human atrial tissue and negative inotropic effects in ventricular tissue in vitro.[13] Thus, with regard to β3-AR agonists, attention is called in the package inserts concerning to their effects on the cardiovascular system, such as blood pressure increased and tachycardia.[14] Therefore, it is necessary to confirm the effects of new β3-AR agonists on the cardiovascular system.

In this study, the safety and efficacy of vibegron, a new β3-AR agonist, were examined in OAB patients aged ≥65 years and aged <65 years, with a focus on the effects on the cardiovascular system and on OAB parameters, using placebo as a control.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a post-hoc subgroup analysis of a randomized, double-blind, placebo-controlled phase 3 study of vibegron (JapicCTI-152936).[15]

2.2 | Subjects

The details of the phase 3 study of vibegron in Japanese patients with OAB were reported elsewhere. Briefly, the inclusion criteria were OAB patients with ≥8 micturitions/d and either ≥1 urgency episodes/d or ≥1 urgency incontinence episodes/d. Patients with urinary tract infection, bladder cancer, bladder calculus, interstitial cystitis, enlarged prostate, residual urinary volume >100 ml, and systolic blood pressure (SBP) ≥ 160 mmHg, diastolic blood pressure (DBP) ≥ 100 mmHg, or pulse rate ≥110 bpm were excluded from the study. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Blood pressure levels and pulse rate were measured in the resting position at each visit.[16] Blood pressure levels and pulse rate were measured in the resting position at each visit.

Among the subjects randomized in the phase 3 study, the present analysis included those who were assigned to receive either vibegron 50 mg (V50), vibegron 100 mg (V100), or placebo for 12 weeks. Subjects were stratified into two subgroups based on age: a <65-year subgroup and a ≥ 65-year subgroup. Patients receiving imidafenacin, the reference drug in the phase 3 study, were excluded (Figure 1).

2.3 | Outcomes

For cardiovascular safety evaluation, analysis was performed on the changes in systolic and diastolic

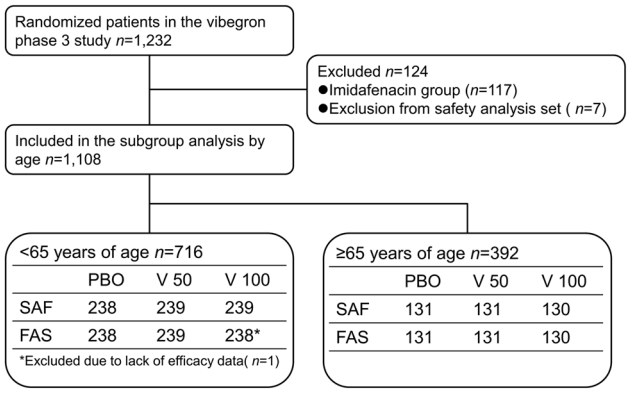

FIGURE 1 Study population. PBO, placebo; V50, vibegron 50 mg; V100, vibegron 100 mg

blood pressure, change in pulse rate, change in residual urine volume, incidence of adverse events for which causal relationship cannot be ruled out, main adverse reactions with an incidence of at least 1%, and number of treatment discontinuations and the reasons.

For efficacy, analysis was performed on the changes from baseline versus placebo in the numbers of micturitions, urgency episodes, and UUI episodes, and the voided volume/micturition.

2.4 | Statistical analysis

Changes in each variable were shown as mean and *SD*. For OAB variables, a constrained longitudinal data analysis model (cLDA[17]) was used to calculate least squares means (LS means) and 95% confidence intervals (CI), and between-intervention comparison was made. The significance level was set at 5% for both sides, and statistical analysis was performed using SAS 9.4 for Windows (SAS Institute Inc.).

TABLE 1 Patient characteristics at baseline (SAF)

	<65 years			≥65 years		
	Placebo	Vibegron 50 mg	Vibegron 100 mg	Placebo	Vibegron 50 mg	Vibegron 100 mg
N	238	239	239	131	131	130
Age, years	51.8 (7.8)	50.9 (7.9)	51.8 (6.9)	71.7 (4.8)	70.9 (4.4)	71.2 (4.6)
Female, *n* (%)	215 (90.3)	211 (88.3)	214 (89.5)	118 (90.1)	123 (93.9)	117 (90.0)
Body weight, kg	58.3 (11.3)	57,3 (11.5)	58.5 (12.2)	54.8 (9.2)	55.6 (10.0)	55.2 (9.8)
BMI, kg/m^2	23.2 (4.3)	22.7 (4.0)	23.0 (4.4)	23.3 (3.3)	23.6 (4.0)	23.4 (3.7)
Hypertension, *n* (%)	53 (22.3)	52 (21.8)	55 (23.0)	53 (40.5)	56 (42.7)	57 (43.8)
Cardiac disorders, *n* (%)	1 (0.4)	0 (0.0)	0 (0.0)	3 (2.3)	2 (1.5)	2 (1.5)
Vascular disorders, *n* (%)	24 (10.1)	23 (9.6)	24 (10.0)	42 (32.1)	46 (35.1)	48 (36.9)
Nocturia, *n* (%)	31 (13.0)	33 (13.8)	40 (16.7)	54 (41.2)	45 (34.4)	54 (41.5)
Nocturnal polyuria index	0.25 (0.08)	0.25 (0.08)	0.25 (0.08)	0.32 (0.11)	0.31 (0.10)	0.32 (0.11)
Duration of OAB, month	57.8 (63.3)	53.9 (52.0)	70.5 (73.7)	58.8 (51.6)	66.2 (79.2)	68.3 (78.0)
Treatment history for OAB, *n* (%)	28 (11.8)	20 (8.4)	31 (13.0)	34 (26.0)	46 (35.1)	31 (23.8)
Number of micturitions/d	11.3 (2.4)	11.2 (2.4)	11.4 (2.3)	10.9 (2.4)	11.0 (2.4)	10.5 (2.0)
Number of urgency episodes/d	4.0 (2.2)	3.8 (2.1)	4.0 (2.3)	3.3 (2.2)	3.4 (2.0)	3.4 (2.2)
Number of UUI/d	1.7 (1.4)	1.6 (1.4)	1.6 (1.2)	1.7 (1.4)	2.0 (1.7)	1.8 (1.6)
Number of nighttime micturitions/d	1.0 (0.8)	1.0 (0.8)	1.0 (0.8)	1.5 (1.1)	1.5 (1.0)	1.4 (1.1)
Voided volume/micturition, ml	156.6 (46.8)	153.5 (45.7)	152.6 (44.7)	159.8 (42.2)	157.0 (44.0)	165.7 (46.6)
Residual urine volume, ml	7.3 (11.7)	6.4 (11.4)	7.5 (11.9)	12.1 (14.8)	8.3 (13.8)	8.1 (12.6)

Note: Mean (*SD*) unless otherwise stated.

Abbreviations: BMI, body mass index; OAB, overactive bladder; SAF, safety analysis set; UUI, urgency urinary incontinence.

3 | RESULTS

3.1 | Subjects

The mean age of the subjects was approximately 51 years in the <65-year subgroup ($n = 716$) and approximately 71 years in the ≥65-year subgroup ($n = 392$) (Figure 1), and females accounted for approximately 90% of all subjects. The percentages of subjects with concomitant hypertension were 22%–23% and 40%–44% in the <65-year and ≥65-year subgroups, respectively. Although there were more subjects with greater nocturnal polyuria index (0.25 vs. 0.31–0.32) and more subjects with treatment history of OAB (8.4%–13.0% vs. 23.8%–35.1%) in the ≥65-year subgroup, there were no notable differences in micturition parameters between the age subgroups. There were eight subjects with cardiac disorders and 207 subjects with vascular disorders (Table 1).

3.2 | Safety

Mean changes in systolic and diastolic blood pressure in the V50, V100, and placebo groups at week 12 were −1.4/−0.4, −2.2/−1.8, and −1.5/−0.9 mmHg in the <65-year subgroup (Figure 2A); and −2.5/−0.7, −2.3/−3.0, and −3.4/−1.6 mmHg in the ≥65-year subgroup (Figure 2B). The results showed no marked change in blood pressure from baseline throughout the study period in the <65-year or the ≥65-year subgroup, and there was no significant difference among the V50, V100, and placebo groups.

Mean changes (*SD*) in the pulse rate in the V50, V100, and placebo groups were −0.9 (8.3), 0.9 (9.6), and −0.3 (8.0) bpm in the in the <65-year subgroup (Figure 2C); and 0.5 (7.4), 0.5 (8.2), and −0.4 (7.8) bpm in the ≥65-year subgroup (Figure 2D). Compared to the placebo group, the change in the pulse rate was significantly higher in the V100 group of <65 years at Week 8 only ($p = .046$), but the absolute difference between the groups was 1.9 bpm, which was not considered clinically meaningful, and disappeared at Week 12.

Mean changes (*SD*) in the residual urine volume in the V50, V100, and placebo groups were 1.2 (14.4), 0.4 (14.2), and −0.1 (13.0) ml in the <65-year subgroup; and 3.2 (15.8), 1.8 (12.9), and 0.6 (17.7) ml in the ≥65-year subgroup. There was no significant difference in the change in residual urine volume among the V50, V100, and placebo groups in either age subgroup.

3.3 | Adverse events

Adverse reactions (adverse events for which causal relationship with the study drug cannot be ruled out)

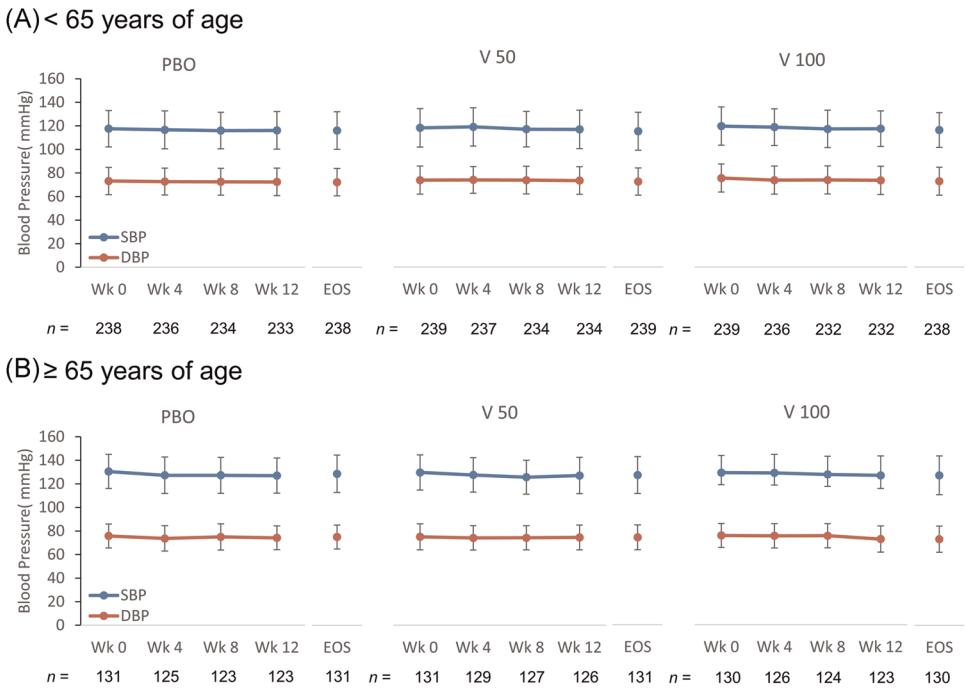

FIGURE 2 Systolic/diastolic blood pressure and pulse rate during the study period. Systolic/diastolic blood pressure at each time point in subjects <65 years of age (A) and ≥65 years of age (B). Changes from baseline in pulse rate in subjects <65 years of age (C) and ≥65 years of age (D). Dots and bars represent mean and *SD*. EOS, end of study; PBO, placebo; V50, vibegron 50 mg; V100, vibegron 100 mg; Wk, week

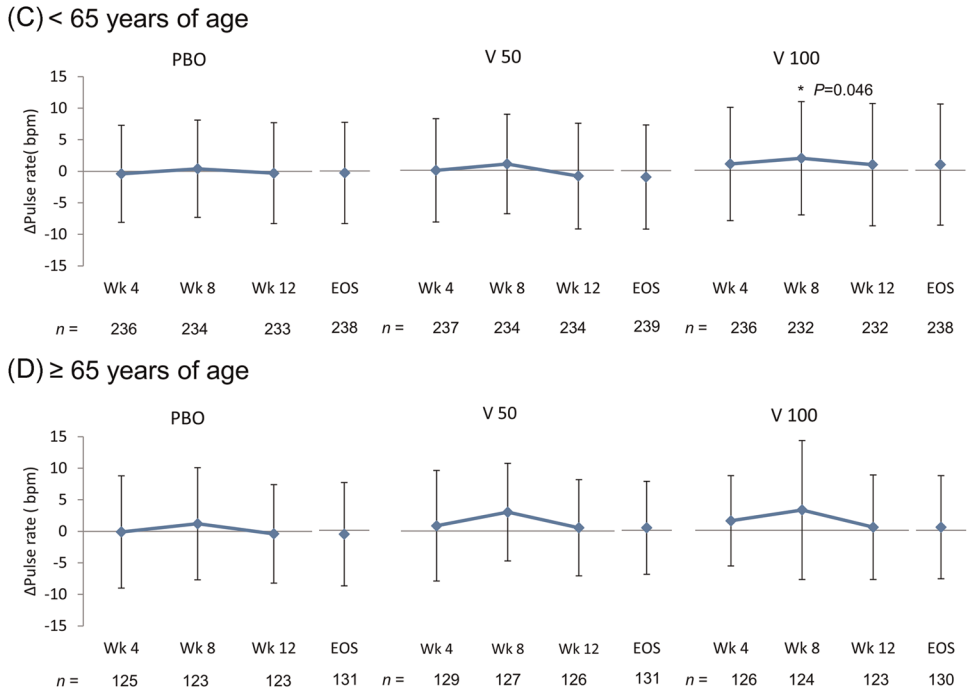

FIGURE 2 Continued

are summarized in Table 2. No serious adverse reactions were reported in either age or treatment group.

Treatment discontinuation due to adverse events occurred in 2 and 1 subjects (<65 years), and 4 and 1 subjects (≥65 years) in the V50/100 and placebo groups, respectively (Table 2).

3.4 | Effects on OAB symptoms

The results showed in all groups, except for urgency episodes in the V50 group aged ≥65 years, a significant change versus placebo in the number of micturitions, the number of urgency episodes, and the number of UUI episodes was achieved in the V50 and 100 groups ($p < 0.05$ for both groups) (Figure 3).

Differences (95% CI) versus placebo group in LS mean change from baseline to week 12 in the voided volume/micturition in the V50 and V100 groups were 20.9 (13.7, 28.1) and 16.3 (9.2, 23.5) in the <65-year subgroup; 34.8 (25.4, 44.1) and 32.5 (23.1, 41.9) ml in the ≥65-year subgroup, demonstrating a significant difference between the two vibegron groups versus placebo group ($p < 0.001$). In addition, the LS mean change in the ≥65-year subgroup was approximately 10 ml greater than that in the <65-year subgroup in both the V50 and V100 groups (Figure 4).

4 | DISCUSSION

There were no significant differences in the cardiovascular outcomes (blood pressure and pulse rate) between the V50/100 and placebo groups in the <65-year or ≥65-year subgroup after 12-week treatment. In the efficacy analysis, V50/100 demonstrated similar efficacy in the <65-year and ≥65-year subgroups; an increasing trend in the voided volume/micturition was observed in subjects aged ≥65 years compared to subjects aged <65 years. No serious adverse reactions were reported in either age group. Treatment discontinuation occurred in two subjects (<65 years), and four subjects (≥65 years) in the V50/100 groups, respectively, one of which was cardiovascular-related (supraventricular tachycardia), observed in the ≥65-year subgroup. These findings suggest that vibegron exerts efficacy in the OAB patients aged ≥65 years with minimal safety concerns.

4.1 | Cardiovascular safety

In the PILLAR study, which investigated the efficacy and safety of a β3-AR mirabegron in 888 patients with OAB and incontinence aged 65 years and older, significant improvements were observed versus placebo in change from baseline in OAB symptoms, and cardiac disorders

TABLE 2 Safety

	<65 years			≥65 years		
	Placebo (*N* = 238)	**Vibegron 50 mg (*N* = 239)**	**Vibegron 100 mg (*N* = 239)**	**Placebo (*N* = 131)**	**Vibegron 50 mg (*N* = 131)**	**Vibegron 100 mg (*N* = 130)**
Adverse reactions, *n* (%)	7 (2.9)	14 (5.9)	8 (3.3)	12 (9.2)	14 (10.7)	12 (9.2)
Main adverse reactions[a], *n* (%)						
Dry mouth	0	3 (1.3)	0	2 (1.5)	2 (1.5)	1 (0.8)
Constipation	2 (0.8)	1 (0.4)	1 (0.4)	0	5 (3.8)	0
Palpitations	0	0	0	0	0	2 (1.5)
Hepatic function abnormal	0	1 (0.4)	0	0	0	2 (1.5)
Low density lipoprotein increased	0	0	0	2 (1.5)	0	0
Treatment discontinuation, *n* (%)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.8)	2 (1.5)	2 (1.5)
Reasons for treatment discontinuation	Acute myeloid leukemia	Neutrophil count decreased	Somnolence	Abdominal pain upper	Oedema, Eczema	Supraventricular tachycardia; Blood creatinine increased; Hepatic function abnormal[b]

[a]Adverse reactions described in the Medical Dictionary for Regulatory Activities (MedDRA) preferred term that occurred in two or more cases in each group.

[b]Adverse event for which a causal relationship with the study drug cannot be ruled out.

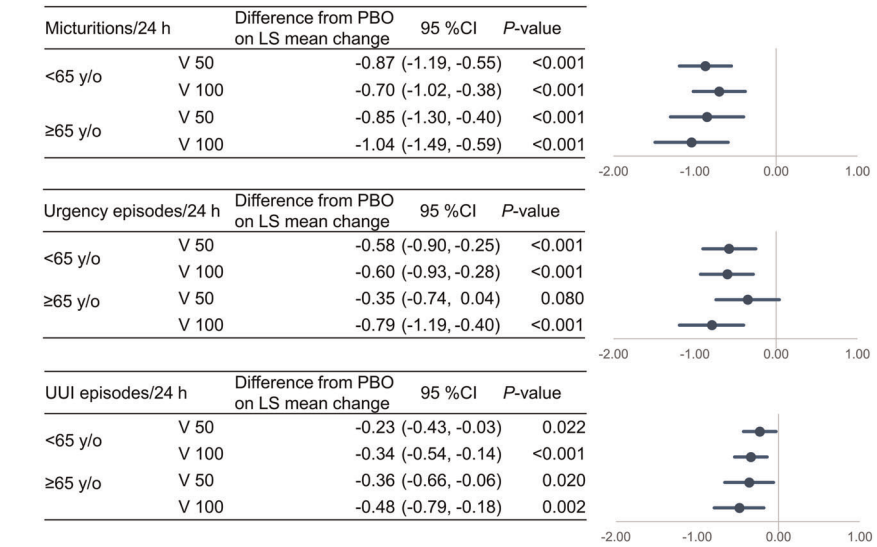

FIGURE 3 Differences versus placebo group in LS mean change from baseline to Week 12 in OAB parameters. Dots and bars represent difference versus placebo in the LS mean change and 95% confidence interval of the difference. LS, least squares; V50, vibegron 50 mg; V100, vibegron 100 mg

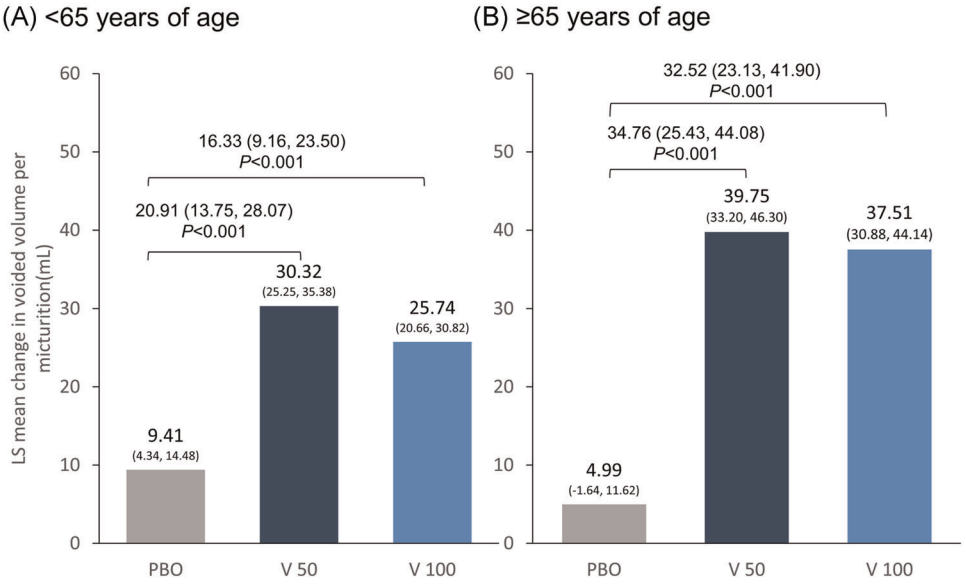

FIGURE 4 LS mean changes from baseline to week 12 in voided volume/micturition. (A) <65 years of age and (B) ≥65 years of age. PBO, placebo; V50, vibegron 50 mg; V100, vibegron 100 mg. LS, least square

were reported in 9 (2.0%) patients treated with mirabegron,[18] confirming mirabegron efficacy, safety, and tolerability in population aged ≥65 years,[19] and the findings with a β3-adrenoceptor agonist mirabegron in the older population were consistent with those in the present study.

Although the present study included patients with cardiovascular diseases, no notable cardiovascular effects were observed with vibegron.

It has been reported that inotropic responses by cardiomyocytes of human right atrium to AR agonists were mediated through β1- and β2-ARs, but not through β3-ARs.[20] Heart failure is characterized by β-adrenergic receptor dysregulation that is primarily due to the up-regulation of G protein-coupled receptor kinases over desensitization of β1- and β2-ARs. While both β1- and β2-ARs exert their action through the coupled G protein, β3-AR, found in the heart, lacks G protein-coupled receptor kinases recognition sites, and is not subject to desensitization.[21] Vibegron was reported to demonstrate excellent selectivity for activation of β3-AR over binding to 1/2-ARs, and there were no additional off-target activities.[22] The cardiac safety profile demonstrated by vibegron in the present study was considered at least partly attributable to its excellent selectivity for activation of β3-AR.

4.2 | Effects on OAB symptoms

In the present study, the subjects aged ≥65 years had a greater increase in the voided volume/micturition than the subjects aged <65 years. Voided volume/micturition is likely to differ between active drug and placebo, and may be a suitable indicator in the evaluation of efficacy. In addition, the V50 group showed a greater increase in voiding volume/micturition than the V100 group. The difference in the change between V50 and V100 groups may have been influenced by the baseline duration of OAB in the <65-year subgroup, and by the baseline average voided volume/micturition in the ≥65-year subgroup. However, we have no definite data to clearly explain the difference in the efficacy observed between V50 and V100 groups. In any case, the differences in the LS mean change between V50 and V100 of about 5 ml in the <65-year subgroup and 2 ml in the ≥65-year subgroup are unlikely to be clinically significant.

In the older population, changes in digestion, absorption, metabolism, and excretion occur, and various functions related to pharmacokinetics and pharmacodynamics are altered. It should also be noted that the magnitude of the effect varies among types of drugs, and that the drugs for renal excretion are more susceptible to the impact of impaired kidney function. Alpha-1 blocker tamsulosin, which is metabolized by CYP3A4 and CYP2D6, has been shown to significantly increase maximum drug concentration (C_{max}) and area under the concentration-time curve (AUC), and to prolong the half-life in healthy adults, when prescribed in combination with the SSRI paroxetine, a potent CYP2D6 inhibitor, or ketoconazole, an antifungal CYP3A4 inhibitor.[17] Mirabegron also increased tamsulosin C_{max}, to 159% (95% confidence interval [CI]: 143%–177%), AUC to 161% (90% CI: 149%–173%), and half-life ($t_{1/2}$) to 116%. Conversely, tamsulosin reduced mirabegron C_{max} to 85% (90% CI: 71%–103%) and AUC to 84% (90%CI: 74%–95%), without effect on $t_{1/2}$.[22] Although in the above studies, no clinically relevant change to safety profile was reported, impact of comorbidities and interaction with other medications should be considered in the practice of OAB in older population.

Vibegron is unlikely to be metabolized by CYP3A4 or CYP2D6 in the liver,[22] and thus is expected to exert its efficacy and safety with fewer interindividual differences among OAB patients regardless of age.

4.3 | Limitations

Approximately 90% of the subjects included in this study were female, and there were few data on male subjects in this investigation. Also, no elderly subjects aged ≥75 years were included. This was a post-hoc analysis of a study with follow-up period of 12 weeks, and further studies on the safety and efficacy of vibegron in patients aged ≥65 years, including male patients with longer-term are needed.

5 | CONCLUSIONS

This post-hoc analysis using phase 3 trial data suggests that vibegron exerts its efficacy on OAB symptoms with minimal influence on cardiovascular parameters in both patients aged ≥65 and <65 years, suggesting that vibegron may be useful in OAB treatment regardless of age.

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CONFLICT OF INTERESTS

Masaki Yoshida has received consultancy fees from Kyorin, grants from Astellas, and speaker fees from Kyorin, Kissei, Astellas, Ferring and Pfizer. Masayuki Takeda has received consultancy fees from Kyorin, grants from Astellas, Asahi-Kasei Pharma, GSK, Nippon Shinyaku, Takeda and Pfizer, and speaker fees from Kyorin, Kissei, Astellas, Daiichi-Sankyo, Nippon Shinyaku, Ono and Pfizer. Momokazu Gotoh has received consultancy fees from Kyorin, Medtronics Japan and Taiho, grants from Kyorin, Kissei, Asahi-Kasei Pharma, Astellas, Chugai, Daiichi-Sankyo, Nippon Shinyaku, Novartis, Ono, Pfizer, Sanofi-Aventis, Taiho and Takeda, and speaker fees from Kyorin, Kissei, Asahi-Kasei Pharma, Astellas, AstraZeneca, Daiichi-Sankyo, Hisamitsu, Nippon Shinyaku, Ono, Pfizer, Sanofi-aventis and Takeda. Osamu Yokoyama has received consultancy fees from Kyorin, Astellas, GSK and Taiho, grants from Kissei, Nippon Shinyaku and Taiho, and speaker fees from Kissei, Astellas, Nippon Shinyaku and Pfizer. Hidehiro Kakizaki has received consultancy fees from Kyorin, Astellas and Taiho, grants from Kissei, Astellas, Daiichi-Sankyo, Nippon Shinyaku, Taiho and Takeda, and speaker fees from Kyorin, Kissei, Astellas, Nippon Shinyaku and Pfizer.Satoru Takahashi has received consultancy fees from Kyorin, grants from Astellas, Nippon

Shinyaku, and speaker fees Kyorin, Kissei, Astellas, Nippon Shinyaku, and Pfizer. Naoya Masumori has received research grants from Astellas, Ono, Daiichi-Sankyo, Takeda, and Kissei, and received lecture fees from Kissei, Janssen, Takeda, Astellas and Astra ZenecaShinji Nagai and Kazuyoshi Minemura are employees of Kyorin.

AUTHOR CONTRIBUTIONS

Masaki Yoshida supervised the study. Masaki Yoshida and Kazuyoshi Minemura contributed to the study concept and design, contributed to acquisition of data, and drafted the manuscript. Masaki Yoshida, Masayuki Takeda, Momokazu Gotoh, Osamu Yokoyama, Hidehiro Kakizaki, Satoru Takahashi, Naoya Masumori, and Kazuyoshi Minemura did analysis and interpretation of data. Shinji Nagai did the statistical analysis. All authors critically revised the manuscript for important intellectual content.

DATA AVAILABILITY STATEMENT

No additional data will be shared.

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