



# Efficacy of Vibegron and Mirabegron for Overactive Bladder: A Systematic Literature Review and Indirect Treatment Comparison

Michael J. Kennelly · Thomas Rhodes · Cynthia J. Girman · Elizabeth Thomas · Denise Shortino · Paul N. Mudd Jr.

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## ABSTRACT

**Background:** In the absence of head-to-head trials, we performed an indirect treatment comparison of the  $\beta_3$ -adrenergic agonists vibegron and mirabegron in the treatment of overactive bladder (OAB).

**Methods:** PubMed, Embase, and Cochrane Library were searched for articles related to phase 3, double-blind, controlled trials of vibegron 75 mg and mirabegron 25/50 mg in patients with OAB. Efficacy outcomes included change from baseline at weeks 4, 12, and 52 in mean daily number of total urinary incontinence episodes and micturitions and mean volume voided/micturition. Effect size was computed as placebo-subtracted change from

baseline (weeks 4, 12) or active control (tolterodine)-subtracted change from baseline (week 52) for each treatment group. Adverse events (AEs) are presented descriptively.

**Results:** After removal of duplicates, 49 records were identified, and after screening 9 met inclusion criteria for analysis. Vibegron showed significantly greater reduction in mean daily number of total incontinence episodes than mirabegron 25 mg at week 4, mirabegron 50 mg (weeks 4, 52), and tolterodine (weeks 4, 12) ( $P < 0.05$ , each) and significantly greater improvement in volume voided versus mirabegron 25 mg (week 12), mirabegron 50 mg (weeks 12, 52), and tolterodine (week 4) ( $P < 0.05$ , each). Confidence intervals of point estimates overlapped zero for all other comparisons of vibegron and mirabegron (25 or 50 mg) or tolterodine, indicating no significant differences between treatments for these time/end-points. Urinary tract infection, hypertension, and dry mouth were the most commonly occurring AEs for vibegron, mirabegron, and tolterodine, respectively, in the short-term trials; hypertension was the most commonly occurring AE with all three treatments in the long-term trials.

**Conclusions:** Vibegron was associated with significant improvement in total incontinence episodes versus mirabegron at 4 and 52 weeks and volume voided at 12 and 52 weeks. Improvement in micturitions was similar between vibegron and mirabegron or

Paul Mudd and Denise Shortino were employees of Urovant Sciences at the time the work was conducted.

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M. J. Kennelly (✉)  
Department of Urology, Obstetrics and Gynecology,  
Carolinas Medical Center, 2001 Vail Ave, Suite 360,  
Charlotte, NC 28207, USA  
e-mail: Michael.Kennelly@atriumhealth.org

T. Rhodes · C. J. Girman  
CERobs Consulting, LLC, Chapel Hill, NC, USA

E. Thomas · D. Shortino · P. N. Mudd Jr.  
Urovant Sciences, Irvine CA USA

tolterodine. Incidence of AEs was generally comparable between vibegron and mirabegron.

**Keywords:** Adrenergic agonists; Urinary bladder; Overactive; Urinary incontinence

### Key Summary Points

#### *Why carry out this study?*

Oral pharmacologic treatments for overactive bladder include anticholinergics and  $\beta_3$ -adrenergic receptor agonists; however, anticholinergics are associated with bothersome side effects and low persistence that may be improved with  $\beta_3$ -adrenergic agonists

In the absence of head-to-head trials for the  $\beta_3$ -adrenergic receptor agonists vibegron and mirabegron as monotherapy, we performed a systematic literature review and indirect treatment comparison of efficacy outcomes from nine clinical trials in patients with overactive bladder

#### *What was learned from study?*

Vibegron was associated with significant improvements in total incontinence episodes compared with mirabegron at weeks 4 and 52 and in volume voided compared with mirabegron at weeks 12 and 52; no significant differences in micturitions were seen between vibegron and mirabegron or tolterodine (active control)

Rates of adverse events were generally comparable between vibegron and mirabegron

Further studies are needed to evaluate whether improved long-term efficacy associated with vibegron in clinical trials translates into improved treatment persistence in real-world settings

## INTRODUCTION

Bothersome symptoms of overactive bladder (OAB) affect an estimated 30 million adults in the USA [1]. Clinical guidelines recommend behavioral therapy with or without pharmacologic management as first-line treatment for OAB and oral anticholinergics or  $\beta_3$ -adrenergic agonists as second-line treatment [2]. However, anticholinergics are associated with adverse effects such as dry mouth, blurred vision, and constipation [3], as well as increased incidence of falls [4] and risk of dementia [5]. Treatment persistence at 12 months with anticholinergics for OAB is poor (~22%) [6], and about 46% of patients cite lack of efficacy as a reason for discontinuing [7].

The introduction of  $\beta_3$ -adrenergic agonists has improved OAB management by minimizing anticholinergic-related adverse effects [8], leading to improved treatment persistence [6] and effectiveness. However, the onset of action of mirabegron—a  $\beta_3$ -adrenergic agonist approved in the USA for the treatment of OAB—may take up to 8 weeks at the recommended 25-mg starting dose or 4 weeks at a 50-mg dose [9], suggesting dose escalation from 25 to 50 mg may be necessary. Furthermore, the maximum dose of mirabegron is 25 mg for patients with severe renal or moderate hepatic impairment [10]. Mirabegron and solifenacin combination therapy can improve long-term efficacy but is associated with increased adverse events (AEs) [11]. Monotherapy with a  $\beta_3$ -adrenergic agonist may be preferred in older patients, those with high anticholinergic burden, and older adults with multiple comorbidities. Vibegron is a selective  $\beta_3$ -adrenergic agonist that was approved by the US Food and Drug Administration at a once-daily dose of 75 mg for the treatment of OAB [12, 13]. Dosage adjustments are not recommended for patients with renal or mild to moderate hepatic impairment [14]. Although both are  $\beta_3$ -adrenergic agonists, vibegron and mirabegron display differing selectivity and maximum response at  $\beta_3$ -adrenergic receptors [15].

Individual, phase 3 clinical trials have compared vibegron 75 mg or mirabegron 25 or

50 mg with placebo and have included anticholinergics as active controls; however, no trial has assessed the comparative efficacy of vibegron versus mirabegron. In such situations, indirect treatment comparisons can be useful to assess differential efficacy between active treatment groups and are commonly used by governing and health technology assessment bodies in the absence of head-to-head trials. We performed a systematic literature review and indirect treatment comparison of efficacy measures for vibegron 75 mg and mirabegron 25 or 50 mg for the treatment of OAB.

## METHODS

### Search and Selection Criteria

This systematic literature review was conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting guidelines. PubMed, Embase, and the Cochrane Library were searched for English language articles using terms related to phase 3, double-blind, controlled trials of vibegron and mirabegron in patients with OAB (Supplementary Table 1). Searches were performed in August 2020. Articles were excluded if they were reviews, pooled analyses, or studies in populations other than OAB (e.g., benign prostatic hyperplasia, neurogenic bladder). A manual search of primary publications and references was performed to identify relevant articles not captured during the initial search. Previously unpublished data for two phase 3 studies of vibegron were provided by Urovant Sciences in the form of clinical study reports; data for the trials have since been published [12, 13].

Article screening was independently conducted by two experienced reviewers who were not involved in manuscript development; discrepancies were resolved by a third reviewer (TR). Titles and abstracts were screened, and if the study reported the outcome of interest and met inclusion criteria, the study was included for full-text review. Studies were included if they were a phase 3, randomized, double-blind, placebo- or tolterodine-controlled trial of

vibegron 75 mg, mirabegron 25 mg, or mirabegron 50 mg for the treatment of patients at least 18 years old with OAB. Studies that included vibegron 50 mg were omitted as the 50-mg dose is not approved in the USA. Studies were required to have at least 3 months' (12 weeks) exposure to study drug.

### Data Extraction and Risk of Bias

One reviewer extracted information on source, study design, population, analysis, interventions, outcome assessments, and results using a standardized extraction form (Supplementary Table 2); a second reviewer verified extracted data against the original publications. Disagreements were resolved by consensus. When more than one publication existed for a study, reports were grouped, and the most recent publication with the most complete data or longest follow-up period was included. Any discrepancies between published versions were recorded.

Two reviewers independently evaluated risk of bias (graded as low, high, or unclear) and quality of the body of evidence (graded as high, moderate, low, or very low) using the Cochrane Risk of Bias Tool [16]. Disagreements were settled by consensus or arbitrated by a third reviewer (TR). Funnel plot asymmetry was examined, and plausible explanations for asymmetry were considered. The "trim and fill" method [17] was used to assess publication bias and estimate the effect corrected for by the bias.

### Outcomes and Data Synthesis

Efficacy outcomes of interest included change from baseline at weeks 4, 12, and 52 in mean daily number of total urinary incontinence episodes, mean daily number of micturitions, and mean volume voided per micturition (in milliliters). Outcomes were based on a 3-day diary for mirabegron (except for a 7-day diary in Herschorn et al. [18]) and 7-day diary for vibegron, which have been shown to give comparable results [19]. Daily total urinary incontinence episodes were defined as the sum of all incontinence episodes in a 24-h period,

averaged across the relevant number of diary days. The definition of urgency and urge urinary incontinence differed among trials and therefore could not be assessed. Forest plots with 95% confidence intervals (CIs) were generated for each outcome measure and time point. For continuous outcomes, mean difference in scores or difference in mean change scores with 95% CIs were derived from summary statistics for each group (i.e., mean or mean change and SD and sample sizes).

Demographics were analyzed in the safety analysis sets (all patients who received at least one dose of study medication) unless otherwise indicated. Micturitions and volume voided were analyzed in the full analysis sets (all patients in the safety analysis set with at least one baseline and postbaseline assessment), and total incontinence episodes were analyzed in the full analysis sets for incontinence (all patients in the full analysis set with at least one incontinence episode at baseline). For weeks 4 and 12, effect size was computed as placebo-subtracted mean change from baseline for each treatment group. Differences between vibegron and mirabegron 25 or 50 mg were computed using the placebo-subtracted mean changes from baseline. Because no placebo group was included in the 52-week vibegron or mirabegron trials, tolterodine 4 mg extended release (active control) was used to compute tolterodine-subtracted change from baseline. For total incontinence episodes and micturitions, negative values indicate improvement (i.e., reduction) from baseline; for volume voided per micturition, positive values reflect improvement. Safety was assessed through AE reporting and is presented descriptively.

Heterogeneity was assessed using 95% prediction intervals; variance of heterogeneity ( $I^2$ ) was calculated for reference. The  $I^2$  statistic measures the inconsistency of study results by describing the percentage of variation across studies that is due to heterogeneity rather than chance. If  $I^2$  was less than 50%, a random effects model was used to create a summary estimate. If  $I^2$  was 50% or more, no summary estimate was produced, and data from individual trials were described. The indirect treatment comparison was conducted using previously described

methods [20]. The Bucher method assumes that the trials indirectly compared are comparable with respect to study population, study design, and outcomes; that the relative treatment effect is the same across the trials; and that pairwise comparisons are independent. It also assumes the log of the effect size measured for drug A versus drug B equals the difference of the log effect size measures, which is supported if assumptions hold. Egger's test is a linear regression of the intervention effect estimates on their standard errors weighted by their inverse variance and was used to identify publication bias in the meta-analyses by assessing asymmetry in a funnel plot. Statistical analyses were performed using Stata, release 16.1 (College Station, TX; StataCorp LLC).

### Compliance with Ethics Guidelines

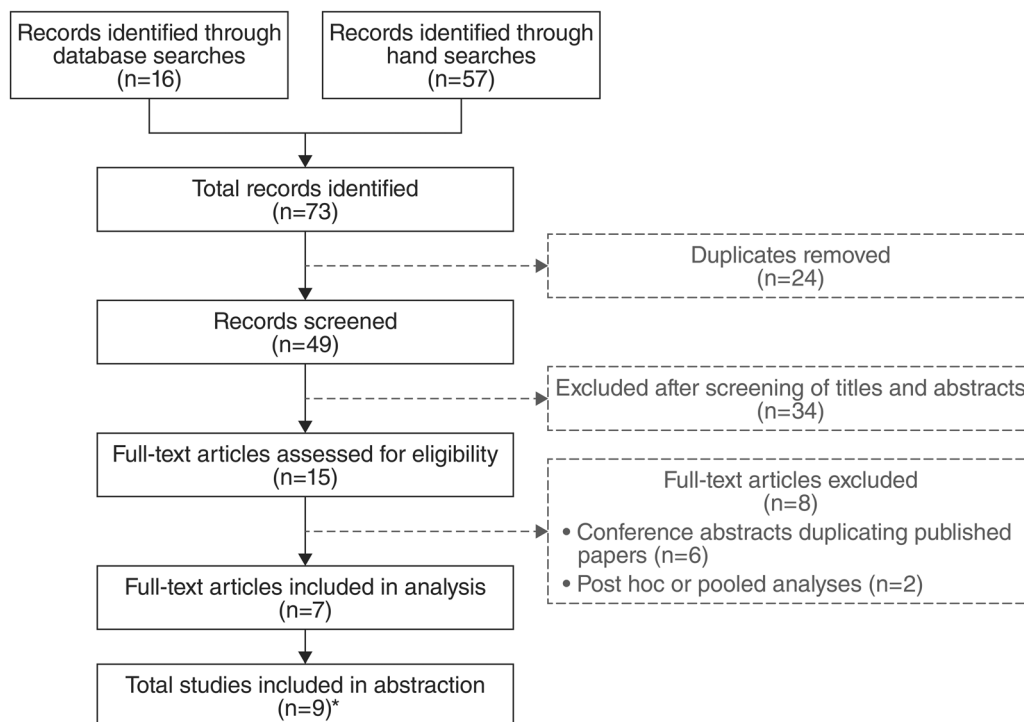
These analyses are based on previously published studies in which ethics approval and informed consent were obtained. As a result, institutional review board approval and written informed consent were not needed.

## RESULTS

### Studies

A total of 16 records were identified through the initial database search, and 57 were identified by hand searches (Fig. 1). After removal of duplicates, 49 records remained and were screened for inclusion; 34 records did not meet inclusion criteria, resulting in 15 full-text articles being assessed for eligibility. After further evaluation, seven were identified and included in the meta-analyses [18, 21–26], in addition to the vibegron phase 3 EMPOWUR [12] and EMPOWUR extension [13] trials.

The nine included trials had similar enrollment criteria, which included patients at least 18 years old with OAB for at least 3 months (at least 20 years old with OAB for at least 24 weeks in Yamaguchi et al. [25]) with or without urinary incontinence. Patients were required to have at least eight micturitions per day and at



**Fig. 1** PRISMA flow diagram. \*Includes two studies that were unpublished at the time in which data were provided by Urovant Sciences

least one [18, 25, 26] or at least three [12, 21–24] urgency episodes. Urgency in the mirabegron trials was typically defined as grade 3 (severe urgency) or 4 (urge incontinence) on the Patient Perception of Intensity of Urgency Scale; in the vibegron trials, urgency was defined as the need to urinate immediately. The trials comprised more than 14,000 patients with OAB; outcomes from more than 10,000 patients were included in the analyses (vibegron,  $n = 526$ ; mirabegron 25 mg,  $n = 855$ ; mirabegron 50 mg,  $n = 3316$ ; tolterodine,  $n = 2425$ ; placebo,  $n = 3020$ ; Table 1). Of the studies, seven were 12-week studies, one was 52 weeks, and one was an extension study of the 12-week trial with up to 52 weeks of exposure. Common comparators for vibegron and mirabegron were placebo and tolterodine (Supplementary Fig. 1).

Baseline demographics were well balanced within trials and were generally similar across trials (Table 1). Mean patient age across all trials ranged from 54.5 to 61.1 years. Most trial participants were women (range 67–85%), and with the exception of trials conducted in Asia,

most participants were white (range 76.6–99.1%). At baseline, mean daily micturitions ranged from 10.8 to 12.6, mean daily incontinence episodes ranged from 1.9 to 4.2, and volume voided/micturition ranged from 145.9 to 165.2 mL (Supplementary Table 3). The percentage of patients with OAB and urinary incontinence ranged from 58.0% to 100%.

## Efficacy Outcomes

### Mean Daily Total Incontinence Episodes

At weeks 4 and 12, all four active treatments had significantly greater reduction from baseline than placebo in total incontinence episodes. At week 52, vibegron had significantly greater reduction than tolterodine (Supplementary Fig. 2). At week 4, vibegron showed significantly greater reduction in mean daily number of total incontinence episodes compared with mirabegron (both doses) and tolterodine ( $P < 0.05$ , each; Fig. 2; Supplementary Table 4). At week 12, vibegron showed significantly greater reduction in total incontinence

**Table 1** Study and patient characteristics (safety analysis sets)

References (trial registration)	Study duration (weeks)	Experimental group*	Control group	Country	Age, mean (SD)	Women, n (%)	Race (white), %
Chappelle et al. [21] (NCT00688688)	52	Mirabegron 50 mg (n = 812)	Tolterodine 4 mg ER (n = 812)	Australia, Canada, Europe, New Zealand, South Africa, USA	59.4 (12.5) <sup>†</sup>	1202 (74.0)	95.9
Herschorn et al. [22] (NCT00912964)	12	Mirabegron 25 mg (n = 432)	Placebo (n = 433)	Europe, North America	59.0 (13.0)	897 (68.7)	90.7
Khullar et al. [23] (NCT00689104)	12	Mirabegron 50 mg (n = 440)	Placebo (n = 494)	Australia, Europe	59.1 (12.5) <sup>†</sup>	1074 (72.5)	99.1
Nirti et al. [24] (NCT00662909)	12	Mirabegron 50 mg (n = 442)	Tolterodine 4 mg ER (n = 495)	Canada, USA	59.7 (13.7) <sup>†</sup>	667 (74.5)	87.8
Yamaguchi et al. [25] <sup>‡</sup> (NCT00966004)	12	Mirabegron 50 mg (n = 369)	Placebo (n = 368)	Japan	58.3 (13.9) <sup>†</sup>	925 (83.7)	NR <sup>§</sup>
Kuo et al. [26] <sup>‡</sup> (NCT01043666)	12	Mirabegron 50 mg (n = 338)	Tolterodine 4 mg (n = 368)	China, India, Korea, Taiwan	54.5 (14.1) <sup>†</sup>	666 (67.0)	NR <sup>¶</sup>
Herschorn et al. [18] (NCT01972841)	12	Mirabegron 25 mg (n = 423)	Placebo (n = 429)	Multinational	57.2 (13.3) <sup>†</sup>	977 (76.7)	79.5
Straskin et al. [12] <sup>‡</sup> (NCT03492281)	12	Mirabegron 50 mg (n = 422)	Placebo (n = 520)	Canada, Europe, USA	60.2 (13.3)	1246 (85.2)	78.3
Straskin et al. [13] (NCT03583372)	52	Vibegron 75 mg (n = 526)	Tolterodine 4 mg ER (n = 417)	USA	61.1 (12.8)	395 (78.2)	76.6

ER extended release, NR not reported

\*Other treatment groups assessed in the trials that were not included in the analyses are not listed in this table

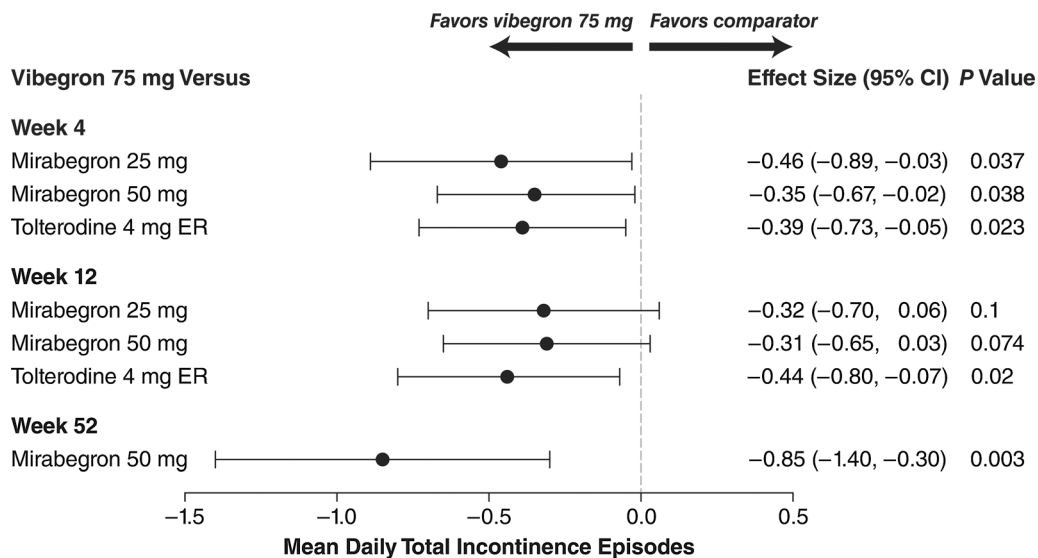
<sup>†</sup> Mean (SD) were derived from the weighted average of relevant subgroups

<sup>‡</sup> Demographics and characteristics based on full analysis set

<sup>§</sup> Study was conducted in Japan; population is assumed to be predominately Japanese

<sup>¶</sup> Study was conducted across sites in China, India, Korea, and Taiwan; population is assumed to be predominately of East or South Asian origin

<sup>||</sup> Study included patients who received placebo in the 12-week trial and were randomized to active treatment during the extension. Patients who received placebo during the 12-week trial were not included in indirect treatment comparison of efficacy outcomes



**Fig. 2** Indirect treatment comparison of change from baseline in mean daily total incontinence episodes (full analysis set for incontinence) based on a 3- or 7-day diary (for mirabegron and vibegron, respectively). Effect sizes at weeks 4 and 12 were calculated using placebo-subtracted

changes from baseline; effect size at week 52 was calculated using tolterodine-subtracted changes from baseline. Negative effect sizes favor vibegron; positive effect sizes favor comparators. *ER* extended release

episodes than tolterodine ( $P < 0.05$ ). At week 52, vibegron showed significantly greater reduction in total incontinence episodes versus mirabegron 50 mg ( $P < 0.01$ ).

### Mean Daily Micturitions

At week 4, all active treatment groups except mirabegron 25 mg had significantly greater reduction from baseline than placebo in micturitions; all active treatments had significantly greater reduction versus placebo at week 12. Neither vibegron nor mirabegron was significantly different than tolterodine at week 52 (Supplementary Fig. 3). Confidence intervals for point estimates overlapped zero for all seven comparisons between vibegron and mirabegron 25 or 50 mg and between vibegron and tolterodine, indicating no statistically significant differences between treatments across all time points (Fig. 3; Supplementary Table 4).

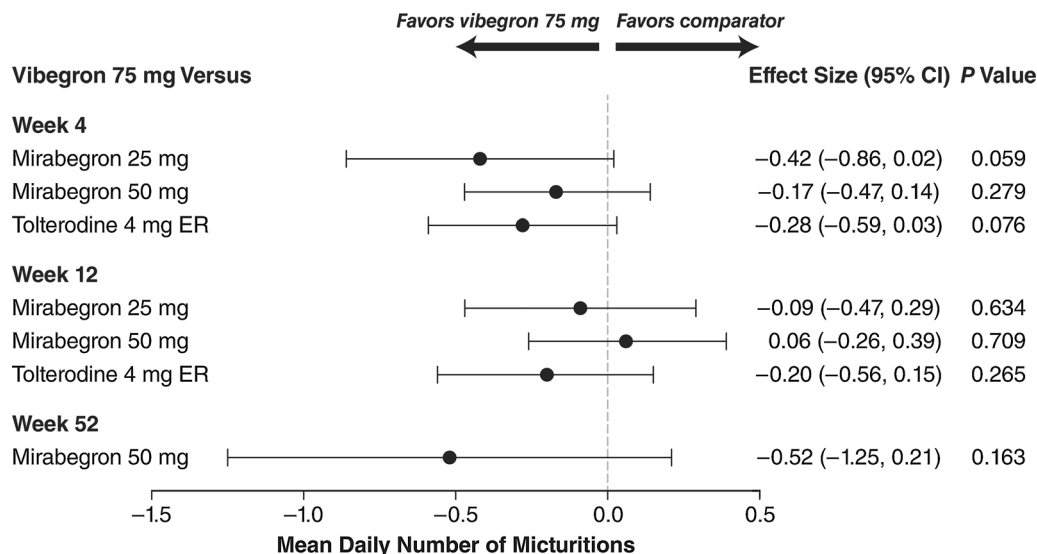
### Volume Voided Per Micturition

At week 4, only vibegron and mirabegron 50 mg had significantly greater improvement from baseline than placebo in volume voided; all active treatments had significantly greater

improvement versus placebo at week 12; and only vibegron had significantly greater improvement than tolterodine at week 52 (Supplementary Fig. 4). Volume voided was not reported for mirabegron 25 mg at 4 or 52 weeks or for tolterodine at 52 weeks. At week 4, vibegron showed significantly greater improvement in volume voided versus tolterodine ( $P < 0.05$ ; Fig. 4; Supplementary Table 4). At week 12, vibegron showed significantly greater improvement in volume voided versus both doses of mirabegron (25 mg:  $P < 0.01$ ; 50 mg:  $P < 0.05$ ). At week 52, vibegron showed significantly greater improvement versus mirabegron 50 mg ( $P < 0.05$ ).

### Heterogeneity

$I^2$  was less than 50% within treatment groups and outcomes, suggesting minimal heterogeneity within treatment groups, with the exception of week 12 values for volume voided per micturition with tolterodine (Cochran's  $Q$   $P = 0.03$ ;  $I^2 = 67\%$ ).



**Fig. 3** Indirect treatment comparison of change from baseline in mean daily micturitions (full analysis set) based on a 3- or 7-day diary (for mirabegron and vibegron, respectively). Effect sizes at weeks 4 and 12 were calculated

using placebo-subtracted changes from baseline; effect size at week 52 was calculated using tolterodine-subtracted changes from baseline. Negative effect sizes favor vibegron; positive effect sizes favor comparators. *ER* extended release

**Risk of Bias**

Egger’s regression test did not detect significant publication bias. Risk of bias was assessed to be low across all studies and criteria, and quality level was assessed as high for all studies.

**Safety**

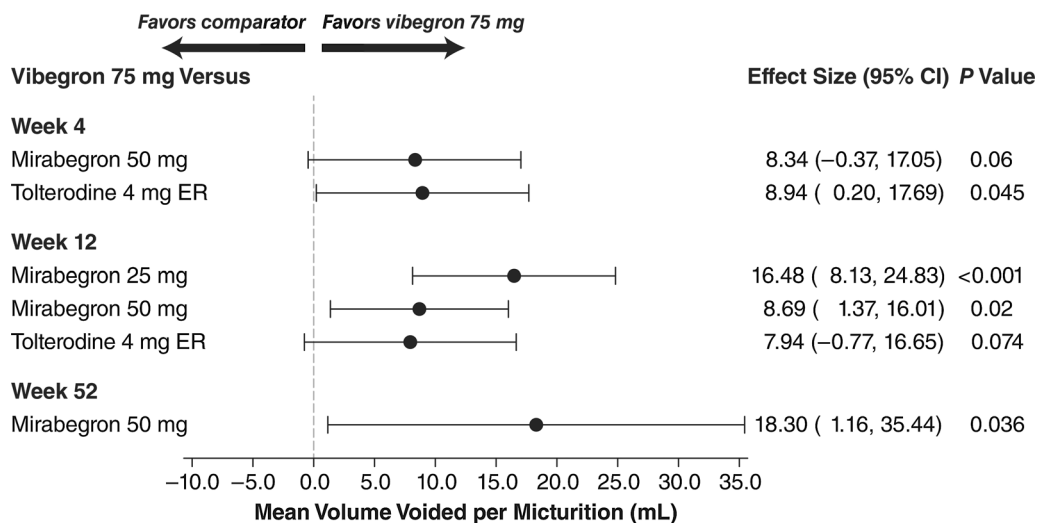
Only the publications by Chapple et al. [21], Herschorn et al. [22], Khullar et al. [23], Nitti et al. [24], Yamaguchi et al. [25], Kuo et al. [26], and Staskin et al. [13] reported the incidence of AEs that occurred in at least 2% of any treatment group. Staskin et al. [12] reported AEs with an incidence of at least 2% in the vibegron group and greater than for placebo. Across all short-term trials reporting such data, the most frequently occurring AE with mirabegron 25 or 50 mg was hypertension (mostly 0.3–11.3% of patients), with vibegron was urinary tract infection (UTI; 5%), and with tolterodine was dry mouth (6.5–13.3%; Supplementary Table 5). In the short-term trials, additional AEs reported at an incidence of at least 5% were nasopharyngitis with mirabegron 50 mg and

hypertension and UTI with tolterodine [12, 22–26]. Across the long-term trials, the most frequently occurring AE with mirabegron 50 mg, vibegron, and tolterodine was hypertension (9.2%, 8.8%, and 8.6–9.6%, respectively; Supplementary Table 6). Additional AEs reported at an incidence of at least 5% were UTI with mirabegron 50 mg; UTI and headache with vibegron; and UTI, dry mouth, and nasopharyngitis with tolterodine [13, 21].

**DISCUSSION**

This indirect treatment comparison assessed the efficacy of vibegron and mirabegron for the treatment of OAB. In the clinical trials, vibegron and both doses of mirabegron showed significant improvement versus placebo in all assessed efficacy measures at week 12. In this indirect treatment comparison, vibegron showed significantly greater improvement in total urinary incontinence episodes versus mirabegron 25 and 50 mg and tolterodine at week 4, versus tolterodine at week 12, and versus mirabegron 50 mg at week 52. Vibegron also showed significantly greater improvement in volume





**Fig. 4** Indirect treatment comparison of change from baseline in mean volume voided per micturition (milliliters; full analysis set) based on a 3- or 7-day diary (for mirabegron and vibegron, respectively). Effect sizes at weeks 4 and 12 were calculated using placebo-subtracted

changes from baseline; effect size at week 52 was calculated using tolterodine-subtracted changes from baseline. Positive effect sizes favor vibegron; negative effect sizes favor comparators. ER extended release

voided versus tolterodine at week 4, versus mirabegron 25 and 50 mg at week 12, and versus mirabegron 50 mg at week 52. For all remaining comparisons, confidence intervals for point estimates for comparisons between vibegron and mirabegron 25 or 50 mg or tolterodine crossed zero, indicating no statistically significant differences among active treatment groups. Both vibegron and mirabegron demonstrated favorable safety profiles across the trials reported. Hypertension was the most frequently occurring AE with mirabegron in the short- and long-term trials, and UTI and hypertension were the most frequently occurring AEs with vibegron in the short- and long-term trials, respectively.

While efficacy data were available for vibegron at week 2 (exploratory endpoint) [12], similar data were not available for mirabegron, and therefore efficacy outcomes at week 4 were analyzed as this was the earliest mutually available time point among all analyzed trials. The indirect comparison at week 4 showed statistically greater improvements for vibegron versus mirabegron 25 and 50 mg for total urinary incontinence episodes. As such, results from this analysis suggest a more rapid onset of

incontinence reduction with vibegron versus mirabegron 25 or 50 mg. Differences in micturitions between vibegron and both doses of mirabegron or tolterodine were not significant at week 4. Similarly, differences in volume voided at week 4 between vibegron and mirabegron 50 mg were not significant. Results at week 12 were generally similar among all active treatment groups and across all three endpoints, with the exception of significantly greater improvement in volume voided with vibegron compared with both doses of mirabegron.

In these analyses, vibegron but not mirabegron 50 mg showed significant improvement versus tolterodine at week 52 for total incontinence episodes and volume voided, suggesting a potential for more durable efficacy for these endpoints. In the indirect comparison, improvement in total incontinence episodes and volume voided was significantly greater for vibegron compared with mirabegron 50 mg at week 52. All active treatment groups showed similar efficacy with regard to micturitions in the individual trials and in this indirect treatment comparison. Because perception of a lack of efficacy is a common reason for discontinuing anticholinergic medication for OAB [7], the

long-term (52-week) efficacy seen with vibegron in randomized controlled trials may translate into improved real-world treatment persistence; however, additional research is needed to fully assess this.

Micturitions and volume voided are standard and generally objective measures used to assess efficacy in OAB clinical trials [27]. Treatment goals include reducing the number of micturitions and increasing volume voided per micturition; however, these measures may not correlate with subjective, patient-reported improvement, and micturitions may be driven by factors outside of pharmacologic manipulation (e.g., fluid intake, voiding out of convenience, rate of bladder filling). Reductions in urgency and incontinence may be associated with improved treatment satisfaction. While significant reductions versus placebo in urgency episodes, when reported, were seen in many of the original trials, definitions for urgency differed among the trials. Therefore, to enable comparison between trials and assess outcomes relevant in real-world settings, total incontinence episodes were incorporated. In this indirect treatment comparison, vibegron showed significantly greater improvement in total incontinence episodes versus placebo and tolterodine across all time points assessed and versus both doses of mirabegron at week 4 and versus mirabegron 50 mg at week 52.

One potential explanation for differences in efficacy between vibegron and mirabegron may be related to selectivity at  $\beta_3$ -adrenergic receptors. One study suggested an approximately 80% maximum binding ( $E_{max}$ ) for the  $\beta_3$  receptor with mirabegron (normalized to isoproterenol) [28]. A separate head-to-head in vitro study also showed an 80%  $E_{max}$  with mirabegron but a higher, approximately 99%  $E_{max}$  with vibegron [15].

To the best of our knowledge, this is the first analysis comparing vibegron with mirabegron in patients with OAB. This indirect treatment comparison used rigorous search criteria and statistical methods and is considered an important contributor to the total body of evidence when comparative clinical trials are not available. However, there are limitations inherent to indirect treatment comparisons. The

analysis included a single study for vibegron for each time point. Consequently, the overall population receiving vibegron was smaller than the population receiving mirabegron. As a result of differences in trial design, the percentage of patients with incontinence and mean number of incontinence episodes varied at baseline. However, analyses were performed using weighted averages of treatment effects across studies and placebo- or tolterodine-adjusted changes from baseline. Additionally, studies used various definitions for the outcomes assessed (using 3- versus 7-day diaries) and, as noted above, differing classification of urgency and urge urinary incontinence episodes, which may bias or skew results. However, 3- and 7-day diaries have demonstrated similar effectiveness in accurately assessing OAB symptoms [19]. Not all outcomes were assessed at all time points. Reporting of safety outcomes differed between trials, and thus the reporting of AEs may not be comprehensive. This analysis is limited by the assumptions of similarity and consistency among trials, as well as the quality of published methods and results. However, all included studies were high-quality randomized controlled trials, strengthening robustness across all time points.

## CONCLUSION

In this indirect treatment comparison of  $\beta_3$ -adrenergic receptor agonists for the treatment of OAB from nine clinical trials, once-daily vibegron 75 mg showed significant improvements at week 4 in total incontinence episodes compared with mirabegron 25 mg, mirabegron 50 mg, and tolterodine and in volume voided compared with tolterodine. At week 12, vibegron 75 mg showed significant improvements in total incontinence episodes versus tolterodine and in volume voided versus mirabegron 25 and 50 mg. Improvements at week 52 with vibegron in total incontinence episodes and volume voided were significantly greater than those with mirabegron 50 mg. No significant differences were seen between vibegron and either dose of mirabegron in daily number of micturitions at any time point. The  $\beta_3$ -

adrenergic receptor agonists vibegron and mirabegron showed similarly favorable safety profiles. Further, in-depth analyses are needed to evaluate comparative safety, and additional research is needed to determine whether improved efficacy in clinical trials translates into improved treatment persistence in real-world settings.

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**Data Availability.** All data generated or analyzed during this study are included in this published article and its supplementary information files.

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