International Phase III, Randomized, Double-Blind, Placebo and Active Controlled Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder: EMPOWUR

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Abbreviations and Acronyms

AE = adverse event
CFB = change from baseline
ER = extended-release
FAS = full analysis set
FAS-I = full analysis set for incontinence
LS = least-squares
OAB = overactive bladder
UUI = urge urinary incontinence

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Purpose: We assessed efficacy, safety and tolerability of vibegron, a novel, potent, highly selective β_3-adrenoceptor agonist, administered 12 weeks at 75 mg once daily to patients with overactive bladder in an international phase III trial with placebo and active control.

Materials and Methods: Adult patients with overactive bladder with 8.0 or more micturitions per day were randomized 5:5:4 to 75 mg vibegron, placebo or extended-release 4 mg extended-release tolterodine. Up to 25% of patients could have dry overactive bladder (less than 1.0 urge incontinence episode per day). Patients completed 7-day voiding diaries at baseline and weeks 2, 4, 8 and 12.

Results: Of 1,518 randomized patients 90.4% completed the trial. At 12 weeks micturitions decreased by an adjusted mean of 1.8 episodes per day for vibegron vs 1.3 for placebo ($p < 0.001$, co-primary end point) and 1.6 for tolterodine. Among incontinent patients urge incontinence episodes decreased by an adjusted mean 2.0 episodes per day for vibegron vs 1.4 for placebo ($p < 0.0001$, co-primary end point) and 1.8 for tolterodine. Moreover, vibegron was statistically significantly superior to placebo for key secondary measures of number of urgency episodes, volume per micturition and proportion of incontinent patients with a 75% or greater reduction in urge incontinence episodes (all $p < 0.01$). Among vibegron treated patients 1.7% discontinued treatment because of adverse events vs 1.1% for placebo and 3.3% for tolterodine. Incidence of hypertension was 1.7% for vibegron and for placebo.

Conclusions: Once daily 75 mg vibegron provided statistically significant reductions in micturitions, urgency episodes and urge incontinence, and increased the volume per micturition. Treatment was well tolerated with a favorable safety profile.

Key Words: adrenergic beta-3 receptor agonists; urinary bladder, overactive; urinary incontinence, urge

PATIENTS with overactive bladder experience episodes of a sudden, compelling desire to void urine, with or without urge incontinence.[1] The age related disorder is common,[2–4] and can negatively impact quality of life.[5,6] For decades anticholinergics have been the chief pharmacotherapy.[7] However, their usefulness is limited by modest efficacy and lack of bladder specificity, leading to well documented side effects including dry

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mouth, constipation and dizziness.[8,9] Moreover, emerging evidence describes an association between cumulative anticholinergic use and risks of cognitive impairment and dementia, with one recent study describing the increased risk (odds ratios range 1.19−1.65) of dementia with bladder anticholinergics.[10] β_3-adrenergic receptors, another potential drug target in OAB,[11,12] have been developed as an alternative oral treatment, and one, mirabegron,[13] has received marketing approval.

Vibegron (RVT-901; KRP-114V)[14,15] is a novel, potent β_3-adrenoceptor agonist with high selectivity in vitro for the β_3 receptor.[16] Vibegron has a long half-life (25 to 38 hours),[17] permitting a once daily formulation, and does not inhibit hepatic CYP2D6.[16] In an international phase IIb dose finding study[17] and in a phase III trial conducted in Japan,[18,19] vibegron showed sustained efficacy vs placebo across all OAB symptoms. During a double-blind treatment period of 8 or 12 weeks,[17,18] followed by 1-year open label extensions,[20,21] vibegron was safe, well tolerated and demonstrated durable efficacy.[17,18,20,21] In EMPOWUR, the international phase III vibegron trial presented here, once daily 75 mg was compared with placebo, with tolterodine extended-release 4 mg as an active control.

MATERIALS AND METHODS

Study Participants

Patients were 18 years old or older with a history of OAB, diagnosed by a physician 3 or more months before screening. All patients also met diary based criteria for either wet or dry OAB (ie urinary urgency with or without urge incontinence). Up to 15% of patients could be male, and 25% or less could have dry OAB. Patients were not enrolled in the study if they had a urine volume output of greater than 3,000 ml.

Study Design

The study consisted of a 1 to 5-week screening period, 28-day washout; 2-week single-blind (patient) placebo run-in; 12-week, double-blind (patients, investigators and sponsor), randomized treatment period; and a 4-week followup safety evaluation.

At screening, patients were trained to use paper diaries. On the 7 days preceding run-in the beginning of double-blind treatment (baseline), and the end of treatment weeks 2, 4, 8 and 12, patients completed a voiding diary, including micturitions, urgency, incontinence and whether incontinence episodes were due to urge or other reasons. On one of the 7 days patients also completed a urine volume diary, recording each measured voided volume that day. For wet OAB (ie urinary incontinence at baseline) each 7-day diary was required to show averages of 8.0 or more micturitions and 1.0 or more urge urinary incontinence episodes per day. For dry OAB, diaries were required to average 8.0 or more micturitions, 3.0 or more urgency episodes and less than 1.0 UUI episodes per day.

By a central, web based interactive response system, patients were randomized at a 5:5:4 ratio, respectively, to oral self-dosing, once daily each morning, of 75 mg vibegron, placebo or 4 mg tolterodine ER. Randomization was stratified by sex and by wet vs dry OAB. Each vibegron dose was accompanied by a placebo capsule matching tolterodine ER, and tolterodine ER by a placebo tablet matching vibegron. The placebo group received both matching placebos.

Efficacy End Points

Two measures were predefined as co-primary end points. 1) Change from baseline to week 12 in the average daily number of micturitions was calculated for each patient. 2) Change from baseline to week 12 in the average daily number of UUI episodes was calculated for each patient with wet OAB.

Among predefined key secondary end points were change from baseline to week 12 in the average daily number of urgency episodes, calculated for each patient; average volume voided per micturition, calculated for each patient from all recorded volumes; and proportion of wet OAB cases with 75% or greater reduction in the average daily number of UUI episodes.

Statistical Analyses

The full analysis set included all unique randomized patients with 1 or more measured CFB in average daily number of micturitions. The FAS for incontinence included all unique randomized wet OAB cases with 1 or more measured CFB in average daily number of UUI episodes. Changes from baseline were assessed for statistically significant differences between active treatment and placebo by a mixed model for repeated measure, with restricted maximum likelihood estimation. The model included terms for treatment, visit, sex, region (U.S. vs nonU.S.), baseline score, interaction between visit and treatment, and (for FAS analyses) OAB category. Responder proportions were assessed by Cochran-Mantel-Haenszel risk difference estimation, stratified by sex, and (for FAS analyses) OAB category. Multiple imputation was used for missing data. To control overall Type-1 error rate at $\alpha = 0.05$ level, co-primary and key secondary end points were tested in a predefined hierarchical order and would stop when $p < 0.05$ was found. The formal efficacy analysis compared vibegron with placebo. All other efficacy end points including comparisons between tolterodine and placebo were considered supportive and were given nominal p values. No multiplicity adjustments were performed. The safety analysis set consists of all patients who received at least 1 dose of the double-blind medication after randomization.

Sample Size Calculation

The study planned to randomize approximately 500 patients to vibegron, 500 to placebo and 400 to tolterodine. If 10% discontinued prematurely the vibegron and placebo groups would each retain approximately 450 patients, of whom an assumed 75% would have wet OAB. These sample sizes had approximately 98% power to detect a between group difference (vibegron vs placebo) of 0.60 in CFB in micturitions per day, assuming a variability estimate of 2.20 (based on a previous vibegron trial[17]), and

approximately 98% power to detect a between group difference of 0.51 in CFB in UUI episodes per day, assuming a variability estimate of 1.68 (based on the same trial[17]), each at a 2-sided 0.05 significance level.

Safety Measures

Adverse events were recorded from informed consent until the followup safety visit, rollover into an extension study or initiation of another OAB intervention. Protocol defined AEs of clinical interest encompassed potential major cardiac or cerebrovascular events; new onset or worsened hypertension (defined as meeting protocol specified criteria at 2 consecutive visits, or as initiation or increase of antihypertensive medication); increased blood pressure (elevations not meeting the criteria for hypertension); AEs consistent with orthostatic hypotension, cystitis, or urinary tract infection; and liver enzyme elevations leading to study drug interruption or discontinuation. Safety measures also included clinical laboratory assessments, vital signs and physical examinations. Safety data were summarized using descriptive statistics.

Ethical Conduct

The study was conducted in conformance with International Conference on Harmonisation requirements for Good Clinical Practice. The study protocol, amendments and written materials provided to patients were approved by the lead institutional review board, Copernicus Group IRB (Cary, North Carolina). Patients provided written informed consent.

RESULTS

Study Participants

Beginning on March 26, 2018, 1,518 patients were randomized at 199 study sites (fig. 1 and supplementary table 1, https://www.jurology.com). Among randomized patients 1,373 (90.4%) completed the 12-week trial, the last on January 7, 2019, and 1,463 patients (96.4%) contributed data for changes in number of micturitions, composing the FAS. Among these patients 1,127 with wet OAB contributed data for changes in number of UUI episodes, composing the FAS-I.

Baseline characteristics were well balanced across treatment groups (table 1). Overall 85.2% of patients were women and 42.9% were 65 years old or older. At baseline FAS patients had a mean (SD) of 11.5 (3.6) micturitions per day, at a mean 150.5

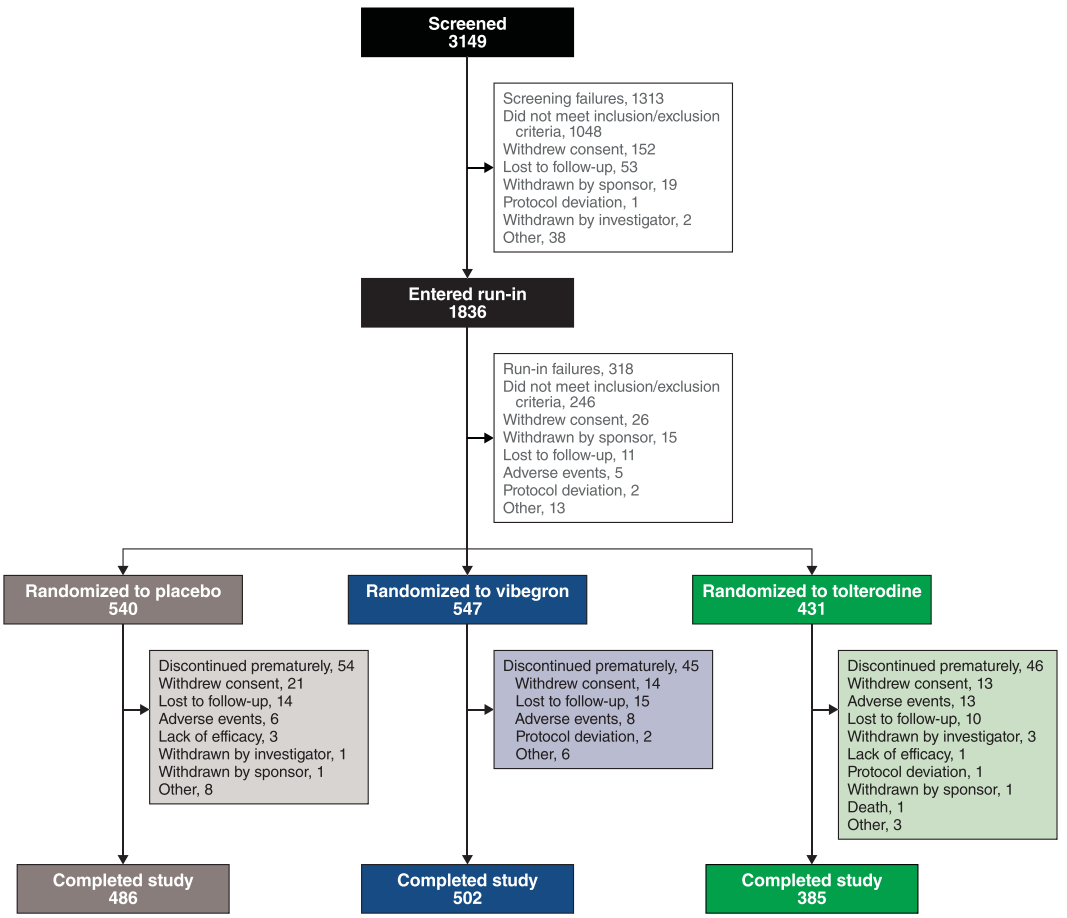

Figure 1. Patient disposition. Nineteen unique patients were screened or randomized at more than 1 study site. Of index cases (earliest instance of screening) 10 were screen failures, 3 cases failed during placebo run-in period and 6 were randomized. Nonindex cases were removed from all analysis sets. Withdrawal by sponsor was primarily due to study compliance at 2 sites.

Table 1. *Baseline characteristics by treatment group (full analysis set)*

	Placebo	Vibegron	Tolterodine
No. pts	520	526	417
Age:			
Median (IQR)	61.0 (16.0)	63.0 (18.0)	61.0 (17.0)
No. 65 or older (%)	220 (42.3)	242 (46.0)	166 (39.8)
No. 75 or older (%)	57 (11.0)	75 (14.3)	47 (11.3)
No. sex (%):			
Female	445 (85.6)	449 (85.4)	352 (84.4)
Male	75 (14.4)	77 (14.6)	65 (15.6)
No. race (%):			
White	406 (78.1)	422 (80.2)	317 (76.0)
Black/African American	79 (15.2)	74 (14.1)	69 (16.5)
Asian	29 (5.6)	27 (5.1)	26 (6.2)
American Indian or Alaska Native	3 (0.6)	1 (0.2)	0
Other	3 (0.6)	2 (0.4)	5 (1.2)
No. region (%):			
U.S.	463 (89.0)	472 (89.7)	376 (90.2)
NonU.S.	57 (11.0)	54 (10.3)	41 (9.8)
OAB category:			
No. wet (%)*	405 (77.9)	403 (76.6)	319 (76.5)
Median UUI episodes/day (IQR)	2.00 (2.57)	2.00 (2.85)	2.00 (2.57)
No. dry (%)	115 (22.1)	123 (23.4)	98 (23.5)
Median micturitions/day (IQR)	10.43 (3.99)	10.43 (3.57)	10.67 (3.73)
Median urgency episodes/day (IQR)	8.00 (5.91)	7.75 (6.21)	8.00 (5.47)
Median ml vol voided/micturition (IQR)	141.7 (76.8)†	150.0 (80.6)‡	143.3 (73.5)§

* Defined as an average of 8.0 or more micturitions and 1.0 or more UUI episodes per day, based on voiding diaries submitted at the beginning of run-in and the beginning of study drug treatment in FAS-I population.
† In 514.
‡ In 524.
§ In 415.

(61.7) ml per micturition, and 8.1 (4.4) urgency episodes per day. FAS-I patients had a mean of 3.5 (2.9) UUI episodes per day.

Co-primary Efficacy End Points

At 12 weeks the least-squares mean CFB in micturition frequency among 492 patients in the vibegron group was −1.8 episodes per day, compared with −1.3 among 475 patients in the placebo group, a LS mean difference of −0.5 (95% CI −0.8, −0.2; p <0.001; fig. 2, *A*). For tolterodine the LS mean 12-week change among 378 patients was −1.6, a LS mean difference of −0.3 from placebo (95% CI −0.6, 0.1; p=0.0988). A statistically significant decrease in adjusted mean change for vibegron vs placebo was already achieved by week 2 (the first observation time point, prespecified exploratory end point), and was maintained at all subsequent exploratory time points.

At 12 weeks the LS mean CFB in UUI episode frequency among 383 patients in the vibegron group was −2.0 episodes per day, compared with −1.4 among 372 patients in the placebo group, a LS mean difference of −0.6 (95% CI −0.9, −0.3; p <0.0001; fig. 2, *B*). For tolterodine the LS mean 12-week change among 286 patients was −1.8, a LS mean difference of −0.4 from placebo (95% CI −0.7, −0.1; p=0.0123). A statistically significant decrease in adjusted mean change for vibegron vs placebo was already achieved by the week 2 exploratory end point and was maintained at all subsequent time points.

Efficacy responses to vibegron in patients with prior OAB pharmacotherapy (anticholinergic or β_3-adrenoceptor agonist) were similar to treatment naïve patients (supplementary table 2, https://www.jurology.com).

Key Secondary Efficacy End Points

At 12 weeks the LS mean CFB in frequency of urgency episodes among 492 patients in the vibegron group was −2.7 episodes per day, compared with −2.0 among 475 patients in the placebo group, a LS mean difference of −0.7 (95% CI −1.1, −0.2; p=0.0020; fig. 3, *A*). For tolterodine the LS mean 12-week change among 378 patients was −2.5, a LS mean difference of −0.4 from placebo (95% CI −0.9, 0.0; p=0.0648). Mean changes were statistically significantly decreased with vibegron vs placebo at the week 2 exploratory end point and all subsequent time points.

At 12 weeks the LS mean change in volume voided per micturition was 23.5 ml among 490 patients in the vibegron group vs 2.2 among 478 patients in the placebo group, a LS mean difference of 21.2 (95% CI 14.3, 28.1; p <0.0001; fig. 3, *B*). For tolterodine the LS mean change was 15.5 among 375 patients and LS mean difference of 13.3 from placebo (95% CI 5.9, 20.7; p <0.001). Mean changes were statistically significantly

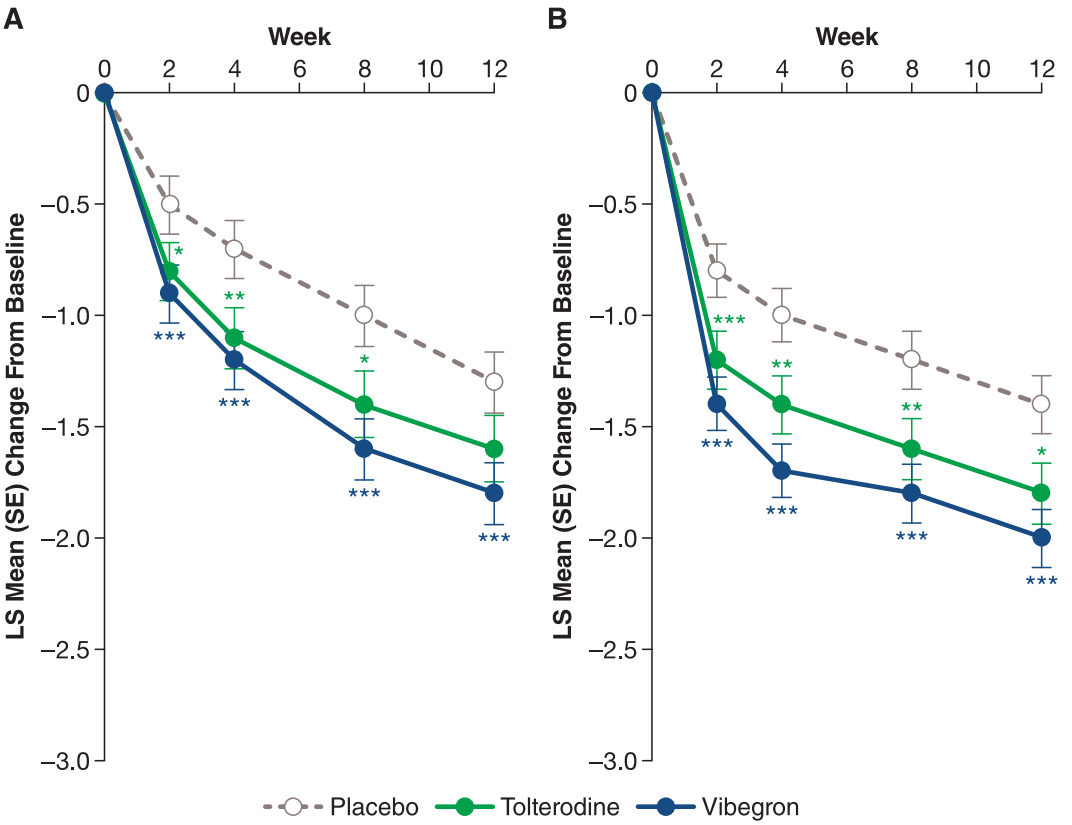

Figure 2. Co-primary end points of LS mean CFB in average number of micturitions per day (*A*, FAS) and in average number of urge incontinence episodes per day (*B*, FAS-I) by treatment group. Calculated as total number of such events on complete diary days, divided by number of complete days. Asterisk indicates p <0.05. Double asterisk indicates p <0.01. Triple asterisk indicates p <0.001 vs placebo, mixed model for repeated measure.

increased with vibegron vs placebo at the week 2 exploratory end point and all subsequent time points.

At 12 weeks the proportion of wet OAB cases with 75% or greater reduction from baseline in UUI episodes per day was 52.4% in the vibegron group vs

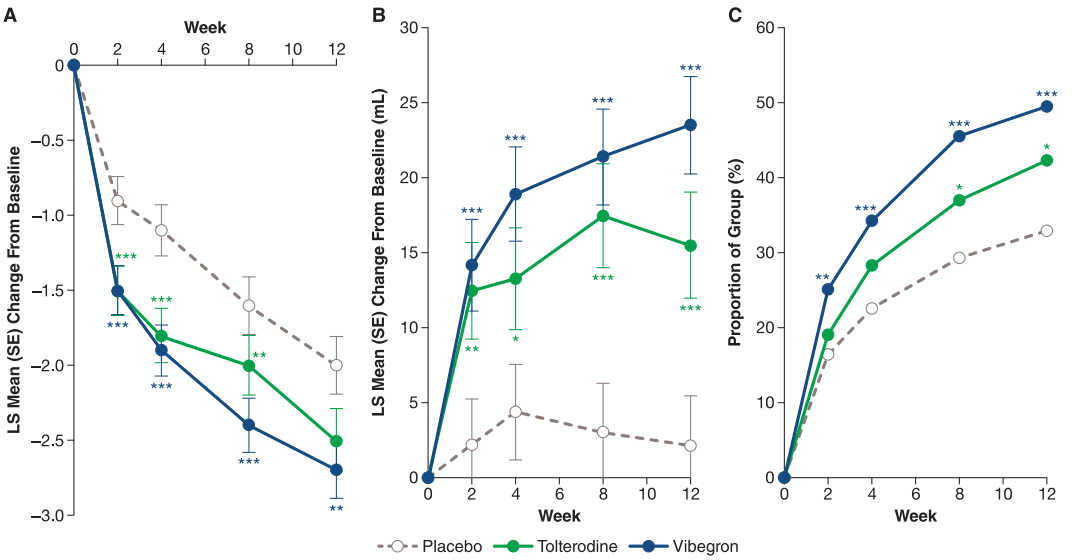

Figure 3. Key secondary end points of LS mean CFB in average number of urgency episodes per day (*A*, FAS), average volume voided per micturition (*B*, FAS) and proportions of wet OAB cases with at least 75% reduction from baseline in urge incontinence episodes per day (*C*, FAS-I), by treatment group. Calculated as total number of such events on complete diary days divided by number of complete days. Asterisk indicates p <0.05. Double asterisk indicates p <0.01. Triple asterisk indicates p <0.001 vs placebo, mixed model for repeated measure (*A, B*) or Cochran-Mantel-Haenszel risk difference estimation (*C*).

Table 2. *Adverse events by treatment group (safety analysis set)*

	Placebo		Vibegron		No. Tolterodine	(%)
No. pts	540		545		430	
No. summary (%):						
Any AE	180	(33.3)	211	(38.7)	166	(38.6)
Any AE of clinical interest	40	(7.4)	36	(6.6)	38	(8.8)
Any serious AE	6	(1.1)	8	(1.5)	10	(2.3)
Any AE leading to treatment discontinuation	6	(1.1)	9	(1.7)	14	(3.3)
No. by AE preferred term (%):*						
Urinary tract infection	33	(6.1)	27	(5.0)	25	(5.8)
Headache	13	(2.4)	22	(4.0)	11	(2.6)
Nasopharyngitis	9	(1.7)	15	(2.8)	11	(2.6)
Diarrhea	6	(1.1)	12	(2.2)	9	(2.1)
Nausea	6	(1.1)	12	(2.2)	5	(1.2)
Upper respiratory tract infection	4	(0.7)	11	(2.0)	2	(0.5)
Constipation	7	(1.3)	9	(1.7)	6	(1.4)
Dry mouth	5	(0.9)	9	(1.7)	28	(6.5)
Hypertension	9	(1.7)	9	(1.7)	11	(2.6)
Dizziness	6	(1.1)	5	(0.9)	4	(0.9)
Blood pressure increased	5	(0.9)	4	(0.7)	8	(1.9)
Urinary retention	2	(0.4)	3	(0.6)	3	(0.7)
Fatigue	5	(0.9)	2	(0.4)	6	(1.4)
Alanine aminotransferase increased	2	(0.4)	1	(0.2)	1	(0.2)
Aspartate aminotransferase increased	1	(0.2)	1	(0.2)	1	(0.2)
Cardiac failure congestive	0		1	(0.2)	0	
Cerebrovascular accident	0		1	(0.2)	1	(0.2)
Cystitis	1	(0.2)	1	(0.2)	1	(0.2)
Hypotension	1	(0.2)	1	(0.2)	1	(0.2)
Blood pressure diastolic increased	0		0		1	(0.2)
Chest pain	3	(0.6)	0		0	
Escherichia urinary tract infection	0		0		1	(0.2)
Pollakiuria	1	(0.2)	0		0	
Syncope	2	(0.4)	0		1	(0.2)

* Includes all AEs with an incidence of 2.0% or greater in the vibegron group and greater than for placebo, plus all protocol defined AEs of clinical interest.

36.8% in the placebo group ($p < 0.0001$; fig. 3, *C*). For tolterodine the proportion was 47.6%. Proportions of patients with 75% or greater reduction were already statistically significantly larger with vibegron vs placebo group at the week 2 exploratory end point and all subsequent time points. Across primary and key secondary end points numerical results were consistently greater for vibegron than for tolterodine.

Safety and Tolerability

During the study 1 patient (tolterodine group) died of stroke, urinary tract infection and sepsis considered unrelated to study drug by the investigator and study sponsor. AEs are summarized in table 2. In the vibegron group the events with an incidence above 2.0% and higher than placebo were headache (4.0% vs 2.4%), nasopharyngitis (2.8% vs 1.7%), diarrhea (2.2% vs 1.1%) and nausea (2.2% vs 1.1%). For tolterodine events with an incidence above 2.0% and higher than placebo were dry mouth (6.5% vs 0.9%), hypertension (2.6% vs 1.7%), headache (2.6% vs 2.4%), nasopharyngitis (2.6% vs 1.7%) and diarrhea (2.1% vs 1.1%). Urinary tract infection was slightly less frequent for vibegron than for placebo or tolterodine (5.0% vs 6.1% and 5.8%, respectively). Incidence of other AEs included hypertension (1.7% for vibegron and for placebo, 2.6% for tolterodine), blood pressure increase (0.7% for vibegron, 0.9% for placebo and 1.9% for tolterodine) and tachycardia (none on vibegron or placebo and 0.2% on tolterodine).

Eight patients (1.5%) in the vibegron group, 6 (1.1%) in the placebo group and 10 (2.3%) in the tolterodine group had AEs that were considered serious. In 2 of these patients, both in the vibegron group, the events (pneumonia and noncardiac chest pain) were classified by the investigator, but not the sponsor, as possibly or probably treatment related. Nine patients (1.7%) in the vibegron group, 6 (1.1%) in the placebo group and 14 (3.3%) in the tolterodine group discontinued study drug due to AEs. Events recorded in 1 or more patients in any group were headache in 6 patients (3 on vibegron, 1 on placebo, 2 on tolterodine), dry mouth, in 4 patients (all on tolterodine), hypertension in 3 patients (1 on vibegron, 2 on placebo) and diarrhea in 2 patients (both on tolterodine).

Laboratory assessments, vital signs and physical examination findings were not associated with any clinically relevant patterns of CFB in any treatment group. There was no clinically relevant difference in posttreatment blood pressure between patients who were hypertensive or nonhypertensive

at baseline (supplementary table 3, https://www.jurology.com).

DISCUSSION

In patients treated with 75 mg vibegron once daily, statistically significant reductions compared with placebo were identified in the number of micturitions and number of UUI episodes per day, already observed at week 2 (first measured time point) and continuing throughout the rest of the 12-week treatment period. For each of 3 other key outcome measures, change in the number of urgency episodes, change in volume per micturition and the proportion of wet OAB cases with a 75% or greater reduction in UUI episodes per day, improvement also was highly statistically significant vs placebo, and was evident at week 2 and all subsequent time points. By all 5 outcome measures improvement was consistently numerically greater than for tolterodine ER.

Throughout the trial vibegron was generally safe and well tolerated with an AE related discontinuation rate similar to placebo (1.7% vs 1.1%). Among AEs of clinical interest the rates of hypertension, increased blood pressure, urinary tract infection and urinary retention were similar to placebo, tachycardia had no reported incidence and dry mouth was less common than for tolterodine. The cognitive risks ascribed to cumulative anticholinergic use[10,22] have not been attributed to β_3-adrenoceptor agonists.

Potential limitations of the present trial include the 12-week duration. However, previous studies of vibegron included 52-week extensions and open label treatment was found to have a good safety/tolerability profile.[20,21] Patients in the present trial could roll over into a 52-week extension study. Moreover, the present trial had numerous strengths, including its recruitment of a large sample of patients with OAB and the assessment of multiple end points important to patients and physicians. The long-term extension, quality of life and other measures will be reported in future publications.

In OAB treatment guidelines intended to maximize symptom control and quality of life and minimize AEs and patient burden, the American Urological Association recommends behavioral therapy as first line treatment and oral pharmacotherapy with a β_3-adrenoceptor agonist or anticholinergic as second line treatment.[23,24] The β3-adrenoceptor agonist mirabegron has demonstrated efficacy and was well tolerated in clinical studies.[13] The present trial expands the evidence that for patients with OAB symptoms, 75 mg vibegron may be a beneficial treatment option.

CONCLUSIONS

In the EMPOWUR phase III study 75 mg vibegron provided statistically highly significant, clinically meaningful improvements in OAB symptoms, including the co-primary end points of reduction in daily micturitions and UUI episodes at 12 weeks, and the important secondary end points of reduction in daily urgency episodes and increase in volume voided per micturition. Statistically significant efficacy began by week 2 and was maintained through week 12. Vibegron was generally safe with AE rates comparable with those for placebo, including the incidence of hypertension.

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EDITORIAL COMMENTS

Mirabegron and anticholinergics have still equal recommendation for OAB treatment.[1] However, anticholinergic recommendation is losing strength. Reasons include low to moderate efficacy, low adherence to treatment and common adverse events, including cognitive dysfunction. In consequence, requests for beta-3 agonist licensing, despite their unclear mechanism of action, will increase. Vibegron is the first beta-3 agonist looking for regulatory authorization after mirabegron introduction.

EMPOWUR is the first pivotal trial studying vibegron in a Western population. It shows that 75 mg once daily is effective already after 2 weeks of treatment, and that efficacy is similar in patients naïve or previously exposed to drugs, including mirabegron. EMPOWUR reinforced the perception that beta-3 agonists are almost free of adverse events in the short term. Hypertension was not detected. Nevertheless, blood pressure control should not be discarded without subanalysis of elderly participants. In a mirabegron database the incidence of hypertension was 1% superior to placebo among patients older than 75 years.[2]

In EMPOWUR the efficacy of vibegron and tolterodine is comparable. Thus, patients receiving vibegron might not meet all their expectations toward OAB improvement. Should physicians cycle such patients into mirabegron or add-on low dose anticholinergics? Answers are needed.

Vibegron will require further studies to clarify efficacy and safety among specific groups, namely men likely to have prostatic obstruction and frail elderly subjects. Long-term studies are necessary and should include cognitive tests. Long-term adherence of vibegron, once licensed, must be estimated.

In conclusion, vibegron is an important mark in OAB treatment but its positioning needs information from additional studies and from real-life use.

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The launch of mirabegron has added β_3-adrenoceptor agonists as a new drug class to the armamentarium for the treatment of overactive bladder syndrome. While one member of this class (ritobegron) has failed to meet its primary end point in phase III clinical trials, solabegron and vibegron are currently undergoing clinical investigation, the latter already being marketed in Japan. While the phase III study underlying the regulatory approval in Japan has been reported earlier (reference 18 in article), Staskin et al now report findings from an international (largely U.S.) phase III study. While the Japanese study tested vibegron doses of 50 and 100 mg per day, the international study applied 75 mg per day. Both studies included a muscarinic receptor antagonist (imidafenacin or tolterodine) as positive control. Irrespective of dose, vibegron reduced number of urgency incontinence episodes and of micturitions more effectively than placebo, whereas the tested muscarinic antagonist was similarly effective as vibegron, an observation also made with mirabegron. Thus, neither β_3-adrenoceptor agonist has proven more effective than a muscarinic antagonist at the group level but the efficacy of the 2 drug classes may vary for individual patients. Similar to mirabegron, vibegron was well tolerated with adverse incidence not much greater than with placebo. A key future research question is whether individual β_3-adrenoceptor agonists differ in efficacy or tolerability. Specifically, it remains to be seen whether the rare but important cardiovascular side effects of mirabegron observed in the post-marketing experience will be shared by all members of this drug class or are specific for mirabegron.[1]

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REPLY BY AUTHORS

We agree with the comments differentiating anticholinergics from β_3 agonists. In addition, vibegron is a novel, potent β_3-adrenoceptor agonist with high selectivity in vitro for the β_3 receptor, a single proposed therapeutic dose (75 mg), and it does not inhibit hepatic CYP2D6,[1] which is particularly important for patients taking additional medications.

With respect to elderly patients, a subanalysis of the adverse event data in this study for those 65 years old or older and 75 years old or older did not reveal a clinically relevant increase in AEs by age group, including hypertension. Percentages of patients with 1 or more treatment emergent adverse events by group assignment for patients 65 years old or older were placebo 37.3% (85 of 228), vibegron 44.7% (110 of 246) and tolterodine 42.7% (73 of 171); percentages for patients 75 years old or older were placebo 40.0% (24 of 60), vibegron 49.3% (37 of 75) and tolterodine 50.0% (24 of 48); and overall study population percentages for patients with 1 or more treatment emergent adverse events were placebo 33.3% (180 of 540), vibegron 38.7% (211 of 545) and tolterodine 38.6% (166 of 430). Of note, neither age group demonstrated an increased incidence of the AE of hypertension (patients 65 years old or older—placebo 3.1%, vibegron 1.2% and tolterodine 2.9%; 75 years old or older—placebo 3.3%, vibegron 1.3% and tolterodine 2.1%; overall study population—placebo 1.7%, vibegron 1.7% and tolterodine 2.6%). Also, there was no increase of the AE of tachycardia.

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