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Platinum Priority – Incontinence – Editor's Choice

Editorial by Christopher R. Chapple on pp. 283–284 of this issue

Vibegron (RVT-901/MK-4618/KRP-114V) Administered Once Daily as Monotherapy or Concomitantly with Tolterodine in Patients with an Overactive Bladder: A Multicenter, Phase IIb, Randomized, Double-blind, Controlled Trial

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Abstract

Background: Antimuscarinics have shown modest efficacy with unwanted side effects in patients with overactive bladder (OAB). Efficacy of vibegron, a new β3-adrenergic receptor agonist, for OAB is unknown.
Objective: To evaluate the efficacy of once-daily oral vibegron in OAB patients (primary), and its safety, tolerability, and efficacy when administered alone or concomitantly with tolterodine (secondary).
Design, setting, and participants: International, phase IIb, randomized, double-blind, placebo- and active comparator–controlled, two-part superiority trial (2011–2013) in OAB-wet or OAB-dry patients aged 18–75 yr (NCT01314872).
Interventions: Part 1: once-daily oral vibegron monotherapy (3 [V3], 15 [V15], 50 [V50], or 100 [V100] mg), tolterodine extended release 4 mg (TER4), or placebo for 8 wk, or combination V50/TER4 for 4 wk and then V50 for 4 wk; part 2: V100/TER4, V100, TER4, or placebo for 4 wk.
Outcome measurements and statistical analysis: Average daily micturitions at week 8 of part 1 (primary); urge incontinence episodes, total incontinence episodes, and urgency episodes (secondary).
Results and limitations: Overall, 1395 patients were randomized. From baseline to week 8, V50 and V100 significantly decreased average daily micturitions (least square mean difference [95% confidence interval], −0.64 [−1.11, −0.18]; $p = 0.007$ and −0.91 [−1.37, −0.44]; $p < 0.001$, respectively) and the number of urge incontinence episodes (−0.72 [−1.11, −0.33] and −0.71 [−1.10, −0.32], respectively; both $p < 0.001$) versus placebo. All vibegron doses were well tolerated. The incidence of dry mouth was higher with TER4 than with vibegron monotherapy. Results are limited by the relatively short treatment duration.
Conclusions: Once-daily V50 and V100 improved OAB symptoms; vibegron was well tolerated as monotherapy and concomitantly with tolterodine. Further development is warranted.
Patient summary: Antimuscarinics, commonly used to treat overactive bladder, produce modest efficacy and unwanted side effects. In this study, a different type of drug (vibegron) was efficacious and safe, alone or with an antimuscarinic (tolterodine).

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1. Introduction

Overactive bladder (OAB), defined as urinary urgency with or without urge incontinence, is generally associated with frequent urination and nocturia in the absence of an infection or other pathology [1]. OAB affects both men and women, and has a substantial negative impact on quality of life [2–4]. Approximately one-third of OAB patients are OAB-wet (with urge incontinence) [5].

Antimuscarinics (eg, oxybutynin, tolterodine, solifenacin, imidafenacin, and fesoterodine), which block postjunctional muscarinic receptors in the detrusor muscle to inhibit muscle contractures, have been the only available OAB pharmacotherapy for decades. Antimuscarinics lack bladder selectivity, resulting in unwanted side effects such as dry mouth, constipation, and central nervous system (CNS) side effects [6–8]. This influences patient satisfaction with treatment, leading to discontinuation, switching, or both [6,9,10]. Although antimuscarinics are most commonly used to treat OAB [10], they are generally not recommended for elderly patients [11], and a large number of OAB patients are elderly. Additionally, chronic use of antimuscarinics is associated with cognitive impairment and dementia [12,13]. Patients intolerant to or unable to use antimuscarinics because of medical contraindications have limited treatment options. Consequently, OAB patients can benefit from effective and well-tolerated drugs that have improved bladder selectivity without the unwanted side effects such as dry mouth and cognitive impairment.

In rat models, β3-adrenergic receptor (β3-AR) agonists relax the detrusor smooth muscle and increase bladder capacity, without influencing the bladder contraction strength needed for emptying [14,15]. In humans, β3-ARs are predominantly expressed in the smooth muscles (eg, bladder detrusor) [15]. The β3-AR agonist mirabegron (Myrbetriq; Astellas Pharma US Inc.) was efficacious and generally well tolerated in multiple phase III trials [16–21] and is approved for OAB treatment in many countries, including Japan [22], the USA [22], and Europe [23].

Vibegron (RVT-901/KRP-114V, formerly MK-4618; Merck Sharp & Dohme Corp.) is a new, potent, and highly selective β3-AR agonist with >9000-fold selectivity for the activation of β3-ARs over β1-ARs or β2-ARs [24]. Favorable preclinical and clinical pharmacokinetic, pharmacodynamic, and toxicological profiles of vibegron support its clinical development as an OAB medication. Notably, vibegron's clinical pharmacokinetic profile and accumulation half-life of 25–38 h support once-daily dosing. Vibegron (alone or concomitantly with tolterodine) was well tolerated in phase I studies, with no serious adverse events (SAEs) or clinically meaningful changes in laboratory parameters or electrocardiograms (ECGs). Tissue distribution studies in animals showed that vibegron does not penetrate into the CNS, suggesting limited potential for CNS toxicity in humans. The efficacy and tolerability of vibegron have also been demonstrated in a phase III trial conducted in Japanese patients with OAB [25].

The objective of this phase IIb trial was to evaluate the safety and efficacy of vibegron as a once-daily oral treatment for OAB patients, regardless of urge incontinence. Additionally, the safety, tolerability, and efficacy of vibegron, administered with or without an antimuscarinic, were evaluated.

2. Patients and methods

2.1. Study design

This randomized, double-blind, placebo- and active comparator–controlled, parallel-group, two-part superiority trial (NCT01314872, Merck protocol 008) was conducted from April 2011 to October 2013 at 169 sites in 18 countries. Parts 1 and 2 were run separately, with part 1 informing the doses of part 2. Each part involved a minimum 1-wk (up to 3 wk as needed) screening, 1-wk placebo run-in, treatment (part 1, 8 wk; part 2, 4 wk), and 2-wk follow-up period (Supplementary Fig. 1). Part 1 included a monotherapy dose-ranging component to assess the efficacy, safety, and tolerability of vibegron alone versus placebo and a concomitant dosing arm (vibegron plus tolterodine extended release [ER]) to assess the proof of concept for combination therapy. In part 2, additional data were collected for vibegron monotherapy and concomitant dosing with tolterodine ER. The trial was approved by appropriate institutional review boards or independent ethics committees, and conducted in accordance with International Conference on Harmonization of Good Clinical Practice and relevant ethical guidelines. All participants provided written informed consent.

2.2. Patients

Patients were aged 40–75 yr in part 1 and 18–75 yr in part 2. Patients were required to have OAB for ≥3 mo before screening, meet predefined OAB-wet or OAB-dry criteria, have a greater number of urge episodes than stress incontinence episodes, and have no clinically significant laboratory or ECG abnormalities. OAB-wet was defined as an average of eight or more micturitions and one or more urgency incontinence episodes per voiding diary day, while OAB-dry was defined as an average of eight or more micturitions, three or more urgency episodes (strong urge to urinate immediately), and less than one daily urgency incontinence episode per voiding diary day. Diuretics, α-adrenergic agonists, serotonin and/or norepinephrine reuptake inhibitors, hormone replacement therapy, or inhaled anticholinergics were permitted at stable doses only, for ≥8 wk before screening visit 1. Patients in part 1 could not participate in part 2. Detailed exclusion criteria are provided in the Supplementary material.

2.3. Screening and placebo run-in periods

After screening, OAB diagnosis was confirmed during the placebo run-in period. Patients recorded occurrences of micturition, urinary urgency episodes (need to urinate immediately), incontinence episodes, and primary reason for incontinence (urge, stress, or other) using a 7-d patient-voiding diary with demonstrated reliability and psychometric properties [26].

2.4. Randomization, blinding, and treatments

For each part of the trial, patients were stratified as OAB-wet or OAB-dry at randomization (visit 3) using an interactive response technology system. The trial was double blinded using in-house blinding procedures; investigators/study staff, patients, and sponsor were all blinded to treatment assignments.

In part 1, patients were equally randomized to receive one of seven treatments (Supplementary Fig. 1). Patients received once-daily vibegron (3 [V3], 15 [V15], 50 [V50], or 100 [V100] mg), tolterodine ER 4 mg (TER4), or placebo for 8 wk or concomitant V50/TER4 for 4 wk, and then V50 for 4 wk. The vibegron dose range in part 1 was based on modeling and simulation results using preclinical and clinical data for vibegron and other β3-AR

agonists. Vibegron dose selection for part 2 was based on the interim results from part 1. In part 2, patients were randomized 2:2:2:1 to receive once-daily V100, TER4, V100/TER4, or placebo for 4 wk (Supplementary Fig. 1). Patients could take the study medications with or without food.

2.5. Outcome measures

Patients completed their voiding diaries for ≥7 d before each visit. Efficacy was assessed in all patients, using the weeks 1, 2, 4, and 8 entries. The primary efficacy endpoint was vibegron dose-related reductions in the least square mean (LSM) daily number of micturitions in all patients at week 8 (part 1). Secondary endpoints included change from baseline to week 4 in LSM daily number of micturitions (part 2). Other secondary endpoints included changes from baseline to week 8 (part 1) and week 4 (part 2) in LSM daily number of total incontinence and urge incontinence episodes (OAB-wet only), and to week 8 (part 1) and week 4 (part 2) in LSM daily number of urgency episodes in all patients. Efficacy and safety were also evaluated in the 52-wk extension of this trial. Exploratory endpoints included results of the King's Health Questionnaire (KHQ).

Safety and tolerability of vibegron, alone or concomitantly with TER4, were monitored throughout the trial. Safety endpoints were assessed using vital signs, ECG, laboratory tests, and a tiered adverse event (AE) reporting approach (Supplementary material).

2.6. Sample size and statistical analyses

Details of sample size determination are provided in the Supplementary material. The full analysis set (FAS; all randomized patients who received one or more doses of study medication and had baseline data or one or more postrandomization observations for the analysis endpoint) was used for analyses of primary and secondary efficacy endpoints. The per-protocol (PP) population was used for supportive analyses of primary and secondary endpoints. The safety population included all patients who received one or more doses of study medication, based on the actual treatment received.

A constrained longitudinal data analysis model was used to analyze primary and secondary efficacy endpoints. The baseline score was entered as a response (dependent) variable in the model with adjustments for treatment, time (weeks), region, and interaction of time (weeks) with treatment (to assess the effect of treatment over time). Each postbaseline measurement was included in the model, and we estimated the change in treatment effect at each postbaseline time point after randomization. Type-I error rate over multiple treatment dose comparisons for the primary endpoint was controlled by a step-down trend test at week 8 only for part 1. Safety data were descriptively summarized. All statistical analyses were performed using SAS v9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

Of 1395 randomized patients (part 1, 987; part 2, 408), 1393 (part 1, 985; part 2, 408) received study medications, and 1324 (94.9%; part 1, 936; part 2, 388) completed the trial (Fig. 1). The

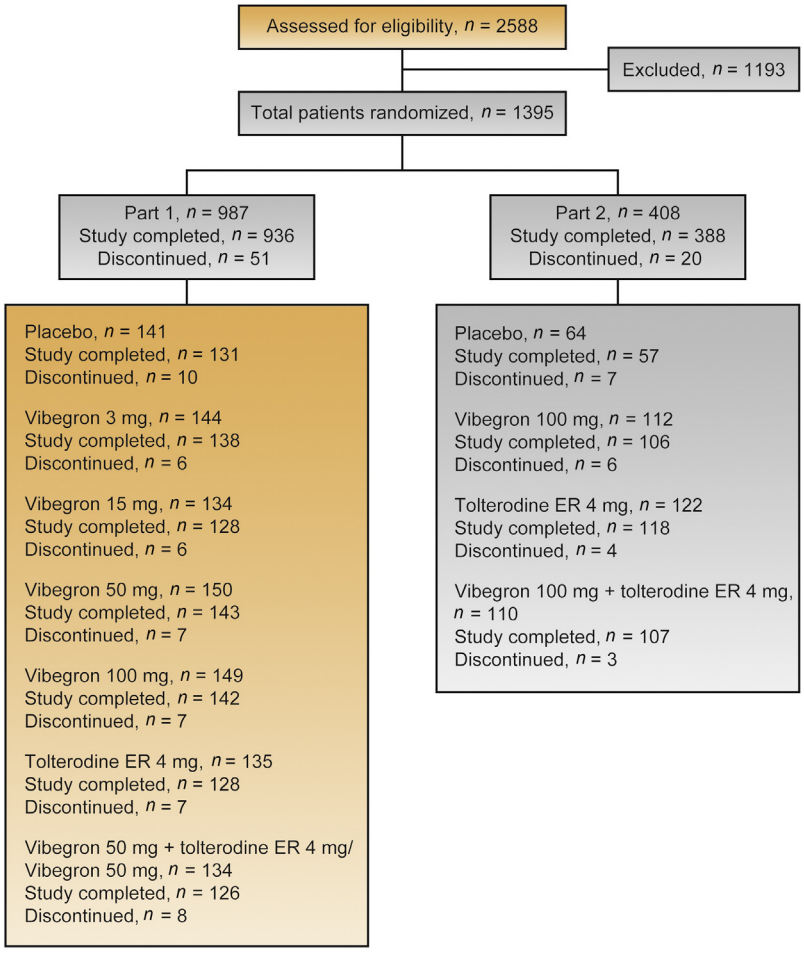

Fig. 1 – Patient disposition. ER = extended release.

Table 1 – Baseline characteristics (parts 1 and 2)

Characteristics	Placebo, *n* (%)	V3, *n* (%)	V15, *n* (%)	V50, *n* (%)	V100, *n* (%)	TER4, *n* (%)	V100 + TER4, *n* (%)	V50 + TER4/V50, *n* (%)	Total, *n* (%)
Total patients	205 (100)[a]	144 (100)	134 (100)	150 (100)	261 (100)[a]	257 (100)	110 (100)	134 (100)	1395 (100)
Gender, women	185 (90.2)	131 (91.0)	125 (93.3)	129 (86.0)	236 (90.4)	231 (89.9)	95 (86.4)	119 (88.8)	1251 (89.7)
Age (yr)									
Mean ± SD	57.8 ± 9.5	59.4 ± 8.7	58.6 ± 8.1	60.3 ± 8.7	59.0 ± 9.2	58.5 ± 9.6	55.5 ± 11.7	59.4 ± 8.5	58.6 ± 9.3
Median	58.0	60.0	59.0	61.0	60.0	58.0	58.0	60.0	59.0
Previously treated with anticholinergic therapy for OAB	64 (31.2)	51 (35.4)	42 (31.3)	63 (42.0)	93 (35.6)	102 (39.7)	45 (40.9)	52 (38.8)	512 (36.7)
OAB stratum, OAB-wet	171 (83.4)	113 (78.5)	111 (82.8)	121 (80.7)	208 (79.7)	203 (79.0)	86 (78.2)	111 (82.8)	1124 (80.6)
Race									
American Indian/Alaska native	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	2 (0.1)
Asian	46 (22.4)	36 (25.0)	30 (22.4)	30 (20.0)	60 (23.0)	69 (26.8)	33 (30.0)	32 (23.9)	336 (24.1)
Black/African American	10 (4.9)	8 (5.6)	5 (3.7)	5 (3.3)	12 (4.6)	10 (3.9)	6 (5.5)	9 (6.7)	65 (4.7)
Multiracial	9 (4.4)	1 (0.7)	0 (0.0)	3 (2.0)	6 (2.3)	7 (2.7)	5 (4.5)	3 (2.2)	34 (2.4)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.1)
White	140 (68.3)	99 (68.8)	97 (72.4)	112 (74.7)	183 (70.1)	171 (66.5)	65 (59.1)	89 (66.4)	956 (68.5)
Region, Japan	37 (18.0)	31 (21.5)	26 (19.4)	29 (19.3)	51 (19.5)	57 (22.2)	27 (24.5)	30 (22.4)	288 (20.6)
Baseline average daily number of micturitions category									
Mild (<9.5)	71 (34.6)	40 (27.8)	44 (32.8)	40 (26.7)	62 (23.8)	74 (28.8)	31 (28.2)	36 (26.9)	398 (28.5)
Moderate (9.5–<11.5)	59 (28.8)	50 (34.7)	42 (31.3)	59 (39.3)	84 (32.2)	90 (35.0)	35 (31.8)	59 (44.0)	478 (34.3)
Severe (≥11.5)	74 (36.1)	54 (37.5)	47 (35.1)	51 (34.0)	115 (44.1)	93 (36.2)	44 (40.0)	39 (29.1)	517 (37.1)
Null	1 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

Null = not evaluable at baseline; OAB = overactive bladder; SD = standard deviation; TER4 = tolterodine extended release 4 mg; V3/15/50/100 = vibegron 3/15/50/100 mg

[a] Parts 1 and 2 combined.

mean (standard deviation) patient age was 58.6 (9.3) yr; 89.7% of the patients were women, 80.6% were OAB-wet, 20.6% were Japanese living in Japan, and 63.3% had never received anticholinergic therapy for OAB (Table 1). No clinically meaningful between-group differences in baseline characteristics were noted. FAS, PP, and safety populations comprised 1388, 1327, and 1393 patients, respectively. Of those randomized, 71 (5.1%) patients discontinued prematurely, with 2.1% discontinuing because of AEs. Discontinuation of study treatment because of AEs was similar across treatment groups (Fig. 1 and Supplementary Table 2).

3.2. *Efficacy*

3.2.1. *Vibegron monotherapy*

In part 1, vibegron (V50 and V100) monotherapy resulted in a significant dose-related decrease in LSM daily number of micturitions from baseline to that at week 8 versus placebo (difference in LSM: −0.64 and −0.91, respectively; both $p < 0.05$; Table 2 and Fig. 2A). Treatment with V50 (part 1) or V100 (parts 1 and 2) also significantly decreased LSM daily number of micturitions from baseline to week 4 (all $p < 0.05$). Furthermore, patients treated with V50 or V100 experienced significant decreases in LSM daily number of urgency episodes from baseline through week 8 (part 1).

Treatment with V50 and V100 significantly decreased average (95% confidence interval) number of daily micturitions (−0.53 [−0.93, −0.12] and −0.52 [−0.93, −0.12], respectively; Fig. 2A) and urgency episodes (−0.61 [−1.18, −0.04] and −0.72 [−1.30, −0.15], respectively; Fig. 2B) more than placebo as early as week 2.

OAB-wet patients exhibited significant reductions in LSM daily number of urge incontinence episodes from baseline to week 8 versus placebo in all but one active treatment group (all except V3 [part 1], $p < 0.05$; Table 2). Furthermore, OAB-wet patients treated with V15, V50, or V100 exhibited a significant decrease in LSM daily number of total incontinence episodes from baseline to week 8 versus placebo. Treatment with V50 and V100 decreased average number of urgency incontinence (−0.66 [−1.02, −0.29] and −0.42 [−0.78, −0.05], respectively; Fig. 2C) and total incontinence episodes (−0.66, [−1.05, −0.27] and −0.43, [−0.82, −0.04], respectively; Fig. 2D) more than placebo as early as week 2.

3.2.2. *Concomitant vibegron and tolterodine ER*

In part 1, concomitant V50/TER4 treatment significantly decreased LSM daily number of micturitions, producing numerical improvements in urgency episodes from baseline to week 4 compared with V50 or TER4 alone (Fig. 2A and 2B). In part 2, concomitant V100/TER4 decreased LSM daily number of micturitions and urgency episodes from baseline to week 4 versus TER4 or V100 alone; the decrease was statistically significant ($p < 0.05$) versus TER4 (Table 3).

Among OAB-wet patients, a numerically greater decrease in LSM daily number of urgency incontinence episodes was

Table 2 – Constrained longitudinal data analysis—change in average daily number of micturitions, urgency incontinence episodes, total incontinence episodes, and urgency episodes from baseline to week 8 in the full-analysis set population (part 1 base study)

			Daily number of events				Change from baseline		Difference from placebo	
			Baseline		Week 8		Week 8		Week 8	
Event	Treatment	*n*	Mean	SD	Mean	SD	Mean	SD	Difference in LS means[a]	*p* value
Micturitions	Placebo	141	10.86	2.84	9.77	2.51	−1.09	2.17		
	V3	144	10.93	2.35	9.35	2.43	−1.56	1.97	−0.46	0.056
	V15	132	11.32	3.48	9.53	2.85	−1.71	2.22	−0.45	0.064
	V50	148	11.21	3.16	9.05	2.28	−1.87	1.78	−0.64	0.007
	V100	148	11.15	2.32	9.02	2.59	−2.11	1.81	−0.91	<0.001
	TER4	134	11.00	2.17	9.24	2.11	−1.73	2.02	−0.54	0.026
	V50 + TER4/V50[b]	134	10.90	2.52	8.86	3.05	−1.99	2.64		
Urgency urinary incontinence episodes[c]	Placebo	118	3.11	2.68	1.71	2.50	−1.34	1.77		
	V3	113	2.70	1.94	1.21	1.68	−1.38	1.38	−0.28	0.167
	V15	111	2.94	2.23	1.12	2.06	−1.81	1.60	−0.57	0.005
	V50	121	2.81	2.06	0.86	1.16	−1.90	1.75	−0.72	<0.001
	V100	122	2.96	2.42	0.84	1.74	−2.05	1.99	−0.71	<0.001
	TER4	100	2.80	2.13	1.15	2.18	−1.67	1.55	−0.46	0.030
	V50 + TER4/V50[b]	111	2.71	1.88	1.06	1.97	−1.66	2.07		
Total incontinence episodes[c]	Placebo	118	3.61	3.26	1.88	2.68	−1.68	2.01		
	V3	113	3.05	2.11	1.38	1.75	−1.56	1.55	−0.18	0.401
	V15	111	3.32	2.44	1.31	2.26	−1.99	1.64	−0.48	0.029
	V50	121	3.10	2.26	1.02	1.40	−2.02	1.82	−0.60	0.005
	V100	122	3.43	2.83	1.12	2.08	−2.26	2.41	−0.58	0.007
	TER4	100	3.08	2.39	1.32	2.38	−1.80	1.47	−0.34	0.140
	V50 + TER4/V50[b]	111	3.15	2.41	1.20	2.28	−1.97	2.45		
Urgency episodes	Placebo	141	6.52	4.37	4.99	3.77	−1.57	3.28		
	V3	144	6.49	3.66	4.68	4.16	−1.69	2.65	−0.18	0.598
	V15	132	6.93	4.69	4.42	4.40	−2.35	2.50	−0.67	0.052
	V50	148	6.43	4.22	3.71	3.76	−2.36	2.35	−0.76	0.024
	V100	148	7.34	4.14	4.22	4.36	−2.98	2.84	−1.24	<0.001
	TER4	134	6.39	3.78	3.91	3.65	−2.52	2.73	−0.94	0.007
	V50 + TER4/V50[b]	134	6.84	3.96	3.94	4.52	−2.84	3.70		

LS = least square; OAB = overactive bladder; SD = standard deviation; TER4 = tolterodine extended release 4 mg; V3/15/50/100 = vibegron 3/15/50/100 mg.
[a] Constrained longitudinal data analysis model included variables for time, region, and interaction of time by treatment. Negative mean treatment differences were in favor of the intervention (vibegron or TER4 as monotherapy) versus placebo.
[b] Patients took V50 + TER4 during the first 4 wk and V50 during the last 4 wk.
[c] For OAB-wet patients only.

observed from baseline to week 4 with concomitant V50/TER4 and V100/TER4 versus V50, V100, or TER4 alone (Fig. 2C and Table 3). Further, a greater decrease in LSM daily number of total incontinence episodes from baseline to week 4 was observed with concomitant V100/TER4 versus V100 alone (numerically) or TER4 alone ($p < 0.05$), and with concomitant V50/TER4 versus V50 or TER4 alone (Table 3).

3.2.3. *Results of exploratory analyses*

In part 1, treatment with V50 or V100 was associated with significant ($p < 0.05$) improvements in four KHQ domains: incontinence impact, role limitations, physical limitations, and severity measures (Supplementary Table 1). In part 2, significant benefits were also observed in two additional domains: social limitations and emotions.

3.3. *Safety*

Of the 1393 patients treated, 43.6%, 15.9%, and 0.6% experienced one or more AEs, drug-related AEs, and SAEs, respectively (Supplementary Table 2), and 2.1%, 1.1%, and 0.1% discontinued treatment because of an AE, a drug-related AE, and an SAE, respectively. No deaths or drug-related SAEs were reported.

Across all treatment groups, the most frequently reported AEs were dry mouth (5.3%), headache (4.2%), urinary tract infection (4.1%), and nasopharyngitis (3.7%; Table 4); the most frequently reported drug-related AEs were dry mouth (4.7%), constipation (2.2%), headache (1.8%), and fatigue (1.1%). The incidence of dry mouth was higher with TER4 monotherapy (8.6%) and concomitant treatment (V50/TER4, 8.2%; V100/TER4, 11.8%) versus vibegron monotherapy (V3, 3.5%; V15, 4.5%; V50, 4.7%; V100, 1.5%) or placebo (2.9%; $p < 0.05$). The proportion of patients with SAEs or who discontinued therapy due to a drug-related AE was equally low across treatment groups (Supplementary Table 2).

4. Discussion

In this phase IIb clinical trial, the efficacy, safety, and tolerability of vibegron (with and without concomitant

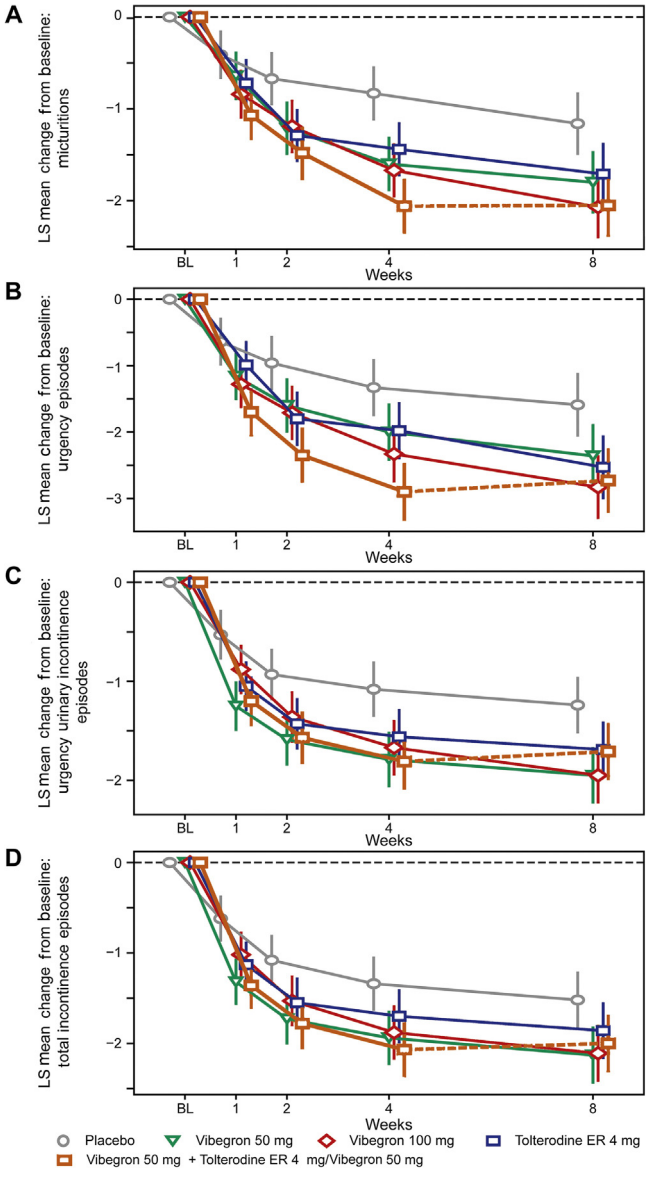

Fig. 2 – Change from baseline in average daily number of (A) micturitions, (B) urgency episodes, (C) urgency urinary incontinence episodes, and (D) total incontinence episodes over 8 wk (part 1; least square mean ± 95% confidence interval). BL = baseline; ER = extended release; LS = least square.

tolterodine) were evaluated in OAB patients. Dose-related reduction in LSM daily number of micturitions was greater with vibegron treatment than with placebo, with statistically significant differences in the 50- and 100-mg dose groups for the primary (micturitions per day) and secondary (micturitions, total and urge incontinence episodes, and urgency episodes per day) endpoints. The magnitude of maximal responses with V50 and V100 was considered clinically relevant and often numerically greater than that with TER4, an approved OAB therapy. These efficacy observations were supported by similar improvements in LSM daily number of urge incontinence episodes, total incontinence episodes, and urgency episodes. In addition, these results provide the proof of concept that concomitant dosing of vibegron and an antimuscarinic can produce modest symptom improvement versus an antimuscarinic alone.

After once-daily vibegron treatment, the placebo-adjusted week 8 changes from baseline in the average number of daily micturitions for V50 and V100 were −0.64 and −0.91, respectively. These results with 8 wk of vibegron monotherapy compare favorably with those reported for mirabegron: placebo-adjusted week 12 changes from baseline in the average number of daily micturitions were −0.45 (25 mg) and −0.64 (50 mg) in a phase II trial [27] and −0.47 (25 mg) and −0.42 (50 mg) in a phase III trial that included both doses [28].

Results of our exploratory analyses demonstrated benefits of V50 and V100 versus placebo on patient-reported outcomes, as exemplified by the results of the KHQ [29]. Treatment with V50 or V100 was associated with significant ($p < 0.05$) improvements in part 1 in four KHQ domains and in part 2 in an additional fifth domain where OAB is known to have detrimental effects. Benefits in some quality of life domains were observed as early as week 4, suggesting that there may be a treatment effect as early as 1 mo after treatment or potentially even earlier.

Vibegron was generally well tolerated. No clinically meaningful differences in the overall incidence or severity of the AEs or drug-related AEs were observed between treatment groups and placebo. The incidence of dry mouth, a typical antimuscarinic side effect, was higher among patients treated with TER4 (alone or concomitantly with vibegron) versus those treated with vibegron monotherapy.

In the 52-wk extension of this trial, once-daily V50 and V100 were generally well tolerated and provided continued improvement beyond the short-term results—clinically relevant reductions in daily micturition, urge urinary incontinence, total incontinence episodes, and urgency episodes at week 52 [30]. The improvement with V100 monotherapy was comparable with the improvement with V100/TER4 combination therapy, while drug-related AEs were more common with V100/TER4.

4.1. *Strengths and limitations*

This multicenter, multiregional, global trial has several strengths: a randomized, double-blind design; a wide vibegron dose range; a relevant active control group (in addition to placebo); and a large and diverse group of OAB patients. Furthermore, a validated voiding diary was used to assess the primary endpoint. A clear dose response for vibegron was demonstrated for the clinical endpoints, further supporting the clinical proof of concept for the treatment of OAB with vibegron. Limitations of this trial include the relatively short treatment duration (up to 8 wk); however, further results from the 1-yr extension of this study will provide additional long-term efficacy and safety assessment. Additionally, this trial was not designed to enable a direct statistical comparison of the magnitude of efficacy benefit for vibegron versus TER4.

Table 3 – Constrained longitudinal data analysis—change in average daily number of micturitions, urgency incontinence episodes, total incontinence episodes, and urgency episodes from baseline to week 4 in the full-analysis set population (part 2 base study)

			Daily number of events				Change from baseline		Difference from placebo[a]	
			Baseline		Week 4		Week 4		Week 4	
Event	Treatment	*n*	Mean	SD	Mean	SD	Mean	SD	Difference in LS means[b]	*p* value
Micturitions	Placebo	64	11.56	3.23	10.65	2.82	−1.20	2.00	NA	
	V100	111	11.88	3.81	9.87	4.34	−1.95	1.90	−0.79	0.009
	TER4	122	11.07	2.30	9.89	2.46	−1.16	1.80	−0.12	0.691
	V100 + TER4	110	11.24	2.94	9.13	2.70	−2.09	2.01		
	Difference from V100								−0.23	0.356
	Difference from TER4								−0.91	<0.001
Urgency urinary incontinence episodes[c]	Placebo	53	3.52	2.52	2.22	2.78	−1.50	1.93	NA	
	V100	86	3.22	2.41	1.50	2.58	−1.71	1.72	−0.24	0.421
	TER4	102	3.29	2.43	1.91	2.71	−1.38	1.85	0.12	0.668
	V100 + TER4	86	2.83	2.04	1.00	1.84	−1.77	1.25		
	Difference from V100								−0.17	0.492
	Difference from TER4								−0.53	0.027
Total incontinence episodes[c]	Placebo	53	4.25	3.43	2.81	3.37	−1.73	1.84	NA	
	V100	86	3.63	2.81	1.65	2.75	−1.98	1.94	−0.39	0.195
	TER4	102	3.76	2.90	2.13	2.84	−1.65	1.90	−0.01	0.984
	V100 + TER4	86	3.24	2.43	1.21	2.03	−1.98	1.39		
	Difference from V100								−0.12	0.626
	Difference from TER4								−0.51	0.038
Urgency episodes	Placebo	64	7.24	3.69	5.02	3.62	−2.35	2.44		
	V100	111	6.53	3.77	3.95	3.68	−2.52	2.67	−0.24	0.530
	TER4	122	6.68	3.71	5.16	4.15	−1.56	2.16	0.76	0.042
	V100 + TER4	110	6.13	3.14	3.36	3.16	−2.68	2.44		
	Difference from V100								−0.27	0.400
	Difference from TER4								−1.27	<0.001

LS = least square; OAB = overactive bladder; SD = standard deviation; TER4 = tolterodine extended release 4 mg; V100 = vibegron 100 mg.
[a] For V100 and TER4 groups.
[b] Constrained longitudinal data analysis model included variables for time, region, and interaction of time by treatment. Negative mean treatment differences were in favor of V100 and TER4 versus placebo (as monotherapy) and in favor of concomitant treatment (V100 + TER4) versus V100 or TER4 monotherapy.
[c] For OAB-wet patients only.

Table 4 – Summary of treatment-emergent adverse events by preferred term incidence 2% in one or more treatment groups: all-subjects-as-treated population (parts 1 and 2 base studies)

	Placebo	V3	V15	V50	V100	TER4	V100 + TER4	V50 + TER4/V50	Total
	n = 205	*n* = 144	*n* = 134	*n* = 148	*n* = 261	*n* = 257	*n* = 110	*n* = 134	*n* = 1393
SOC/preferred term	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Eye disorders									
Dry eye	6 (2.9)	2 (1.4)	1 (0.7)	1 (0.7)	0 (0.0)	3 (1.2)	3 (2.7)	2 (1.5)	18 (1.3)
Gastrointestinal disorders									
Constipation	5 (2.4)	5 (3.5)	6 (4.5)	6 (4.1)	2 (0.8)	5 (1.9)	4 (3.6)	6 (4.5)	39 (2.8)
Diarrhea	5 (2.4)	4 (2.8)	2 (1.5)	1 (0.7)	5 (1.9)	9 (3.5)	1 (0.9)	6 (4.5)	33 (2.4)
Dry mouth	6 (2.9)	5 (3.5)	6 (4.5)	7 (4.7)	4 (1.5)	22 (8.6)	13 (11.8)	11 (8.2)	74 (5.3)
Nausea	3 (1.5)	2 (1.4)	2 (1.5)	3 (2.0)	3 (1.1)	6 (2.3)	0 (0.0)	2 (1.5)	21 (1.5)
General disorders and administration site conditions									
Fatigue	1 (0.5)	4 (2.8)	6 (4.5)	5 (3.4)	2 (0.8)	6 (2.3)	2 (1.8)	2 (1.5)	28 (2.0)
Infections and infestations									
Nasopharyngitis	14 (6.8)	3 (2.1)	7 (5.2)	8 (5.4)	10 (3.8)	4 (1.6)	2 (1.8)	3 (2.2)	51 (3.7)
Sinusitis	2 (1.0)	0 (0.0)	2 (1.5)	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	4 (3.0)	10 (0.7)
Urinary tract infection	7 (3.4)	5 (3.5)	5 (3.7)	8 (5.4)	8 (3.1)	12 (4.7)	5 (4.5)	7 (5.2)	57 (4.1)
Injury, poisoning, and procedural complications									
Accidental overdose	2 (1.0)	3 (2.1)	6 (4.5)	4 (2.7)	11 (4.2)	6 (2.3)	1 (0.9)	2 (1.5)	35 (2.5)
Investigations									
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	3 (2.2)	4 (0.3)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.2)	4 (0.3)
Musculoskeletal and connective tissue disorders									
Arthralgia	2 (1.0)	0 (0.0)	2 (1.5)	3 (2.0)	0 (0.0)	3 (1.2)	1 (0.9)	0 (0.0)	11 (0.8)
Osteoarthritis	1 (0.5)	2 (1.4)	1 (0.7)	4 (2.7)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)
Pain in extremity	0 (0.0)	2 (1.4)	0 (0.0)	2 (1.4)	1 (0.4)	1 (0.4)	3 (2.7)	2 (1.5)	11 (0.8)
Nervous system disorders									
Dizziness	5 (2.4)	1 (0.7)	6 (4.5)	3 (2.0)	7 (2.7)	5 (1.9)	3 (2.7)	1 (0.7)	31 (2.2)
Headache	9 (4.4)	3 (2.1)	6 (4.5)	6 (4.1)	12 (4.6)	9 (3.5)	7 (6.4)	6 (4.5)	58 (4.2)
Renal and urinary disorders									
Dysuria	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	3 (1.2)	3 (2.7)	0 (0.0)	8 (0.6)

SOC = system organ class; TER4 = tolterodine extended release 4 mg; V3/15/50/100 = vibegron 3/15/50/100 mg.

5. Conclusions

The efficacy and safety of once-daily oral vibegron in treating OAB, with or without incontinence, was clearly demonstrated in this phase IIb trial. Vibegron was well tolerated, and the observed efficacy results support further study of vibegron for the treatment of OAB.

Author contributions: Tara L. Frenkl had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.006.

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