GEMTESA® (vibegron)
Phase 3 EMPOWUR Trial
Prior OAB Pharmacotherapy

GEMTESA® (vibegron) is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults.[1] Please see accompanying full Prescribing Information.

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Summary

- The 12-week phase 3 trial demonstrated once-daily vibegron 75 mg provided statistically significant reductions in daily micturitions, urge urinary incontinence (UUI), episodes of urgency, and increased the volume of urine per micturition relative to placebo. Among adverse events (AEs) of clinical interest, the rates of hypertension, increased blood pressure, urinary tract infection and urinary retention were similar to placebo.[2]
    - AE incidence of hypertension (1.7% for both vibegron and placebo), blood pressure increase (0.7% for vibegron, 0.9% for placebo), urinary tract infection (5.0% for vibegron, 6.1% for placebo), urinary retention (0.4% for vibegron, 0.6% for placebo).
- Efficacy responses to vibegron in patients with prior anticholinergic or beta 3-adrenoceptor agonist pharmacotherapy were similar to treatment naïve patients.[2]

Phase 3 EMPOWUR Trial

This international, randomized, double-blind, placebo- and active-controlled study enrolled adult subjects with wet or dry OAB (urinary urgency with or without urge incontinence).[1] Up to 15% of subjects could be male and ≤25% could have dry OAB. Subjects with a daily urine volume output >3,000 mL were excluded. The study consisted of a 1- to 5-week screening period; a 28-day washout period; a 2-week single-blind (subject) placebo run-in period; a 12-week randomized, double-blind treatment period; and a 4-week follow-up safety evaluation.[2]

Subjects completed a voiding diary during the 7-day baseline preceding the double-blind treatment phase and at the end of treatment Weeks 2, 4, 8 and 12 which included micturitions, UUI, urgency, and whether incontinence episodes were due to urge or other reasons. On one of the 7 baseline days, subjects also completed a daily urine volume diary. For wet OAB (urinary incontinence at baseline), each 7-day diary required an average of ≥8.0 daily micturitions and ≥1.0 urge urinary incontinence episodes. For dry OAB, diaries required an average of ≥8.0 daily micturitions, ≥3.0 urgency episodes and <1.0 urge urinary incontinence episode.[2]

Subjects were randomized 5:5:4 to receive vibegron 75 mg, placebo or tolterodine extended release (ER) (active control) 4 mg tablet each morning. Randomization was stratified by gender and by wet or dry OAB. Vibegron was administered with a tolterodine ER (active control) placebo, tolterodine ER (active control) was administered with a vibegron placebo and the placebo group received both placebos. Two predefined co-primary end points were change from baseline in the average daily number of micturitions at Week 12 and the change from baseline

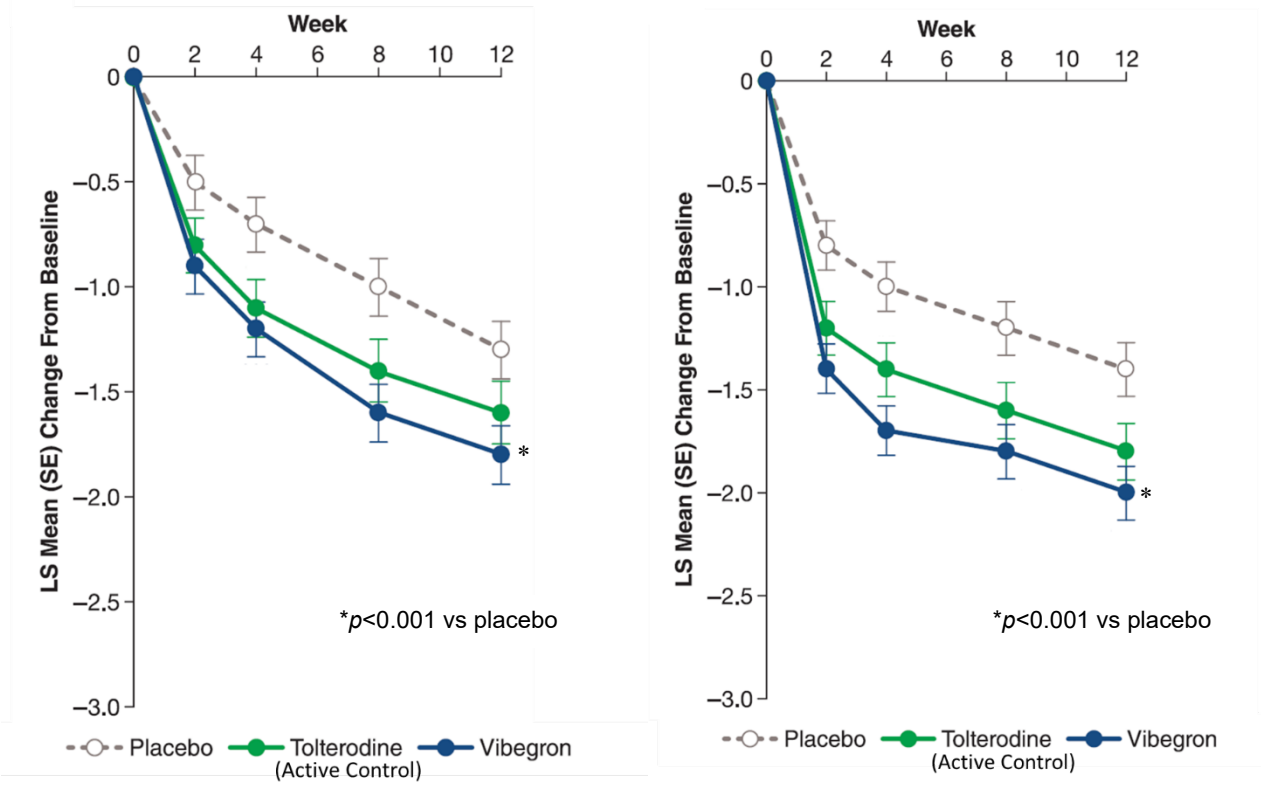
in the average daily number of UUI episodes for subjects with wet OAB at Week 12. Predefined key secondary end points were change from baseline in the average number of baseline daily urgency episodes for each subject at Week 12, average urine volume voided per micturition and the proportion of wet OAB cases with ≥75% reduction in the average number of daily urinary incontinence episodes. Safety measures included clinical laboratory assessments, vital signs, physical examinations and adverse events.[2]

Among randomized subjects (*N*=1,518), 90.4% completed the 12-week trial. Baseline characteristics were well-balanced across treatment groups. Most subjects (85.2%) were female and 42.9% were ≥65 years old. At baseline, subjects in the full analysis set (FAS) had an average and standard deviation (SD) of 11.5 (3.6) daily micturitions with an average 150.5 (61.7) mL per micturition, and 8.1 (4.4) daily urgency episodes per day. Subjects in the FAS for incontinence had an average of 3.5 (2.9) daily urge urinary incontinence episodes.[2]

Co-primary Endpoints

At Week 12, the least squares mean (LSM) change in baseline in daily micturition frequency among subjects in the vibegron group (n=492) was -1.8 episodes vs -1.3 among subjects in the placebo group (n=475), a LSM mean difference of -0.5 (95% CI -0.8, -0.2; *p*<0.001). Among tolterodine-treated (active control) subjects (n=378), the LSM change was -1.6, a LSM difference of -0.3 vs placebo (95% CI -0.6, 0.1; *p*=0.0988) (Figure 1). Efficacy was observed within 2 weeks through week 12.[2]

Figure 1. Least Squares Mean Change in Baseline Number of Daily Micturitions (left) and in Mean Daily Urge Incontinence (UUI) Episodes (right).



At Week 12, the LSM change in daily urge urinary incontinence episode frequency among subjects in the vibegron group (n=383) was -2.0 episodes vs -1.4 for subjects in the placebo group (n=372), a LSM difference of -0.6 (95% CI -0.9, -0.3; *p*<0.0001). For tolterodine (active

control) group (n=286), the LSM 12-week change was -1.8, a LSM difference of -0.4 from placebo (95% CI -0.7, -0.1; *p*=0.0123) (Figure 1). Efficacy was observed within 2 weeks through week 12.[1]

Efficacy responses to vibegron in patients with prior anticholinergic or beta 3-adrenoceptor agonist were similar to treatment naïve patients.[2] (see Table 1)

Table 1. Co-primary efficacy outcomes among patients with versus without prior OAB pharmacotherapy,[a] by treatment group (FAS or FAS-I, observed cases)[3]

Outcome measure, mean (SD)	Treatment group		
	Placebo	**Vibegron**	**Tolterodine (active control)**
Micturitions/day[b] **(FAS)**			
Prior anticholinergic use			
n at baseline	85	77	51
Baseline value	11.1 (3.0)	11.7 (3.3)	11.2 (2.6)
n at 12 weeks	79	74	48
Mean change from baseline	–1.3 (2.3)	–2.0 (2.4)	–1.5 (1.9)
No prior anticholinergic use			
n at baseline	435	449	366
Baseline value	11.9 (4.2)	11.3 (3.4)	11.5 (3.2)
n at 12 weeks	396	418	330
Mean change from baseline	–1.7 (2.8)	–2.1 (2.6)	–1.8 (2.7)
Prior mirabegron use			
n at baseline	27	21	32
Baseline value	10.4 (2.5)	11.2 (2.8)	11.0 (3.2)
n at 12 weeks	25	18	31
Mean change from baseline	0.0 (2.2)	–2.8 (3.8)	–1.3 (2.0)
No prior mirabegron use			
n at baseline	493	505	385
Baseline value	11.8 (4.1)	11.3 (3.4)	11.5 (3.2)
n at 12 weeks	450	474	347
Mean change from baseline	–1.7 (2.7)	–2.0 (2.5)	–1.8 (2.7)
UUI episodes/day[b] **(FAS-I)**			
Prior anticholinergic use			
n at baseline	74	64	42
Baseline value	3.2 (2.3)	2.9 (2.4)	3.4 (2.2)
n at 12 weeks	68	64	39
Mean change from baseline	–0.8 (2.2)	–1.5 (2.2)	–1.0 (1.8)

Outcome measure, mean (SD)	Treatment group		
	Placebo	Vibegron	Tolterodine (active control)
No prior anticholinergic use			
n at baseline	331	339	277
Baseline value	3.6 (3.2)	3.5 (3.0)	3.4 (2.7)
n at 12 weeks	304	319	247
Mean change from baseline	–1.6 (2.4)	–2.1 (2.5)	–1.9 (2.4)
Prior mirabegron use			
n at baseline	23	16	19
Baseline value	2.6 (1.7)	2.6 (1.9)	2.3 (1.1)
n at 12 weeks	21	14	18
Mean change from baseline	–0.3 (1.6)	–1.6 (2.6)	–0.7 (1.4)
No prior mirabegron use			
n at baseline	382	387	300
Baseline value	3.6 (3.1)	3.5 (2.9)	3.5 (2.6)
n at 12 weeks	351	369	268
12-week change	–1.5 (2.4)	–2.0 (2.5)	–1.8 (2.3)

[a]During the prior 12 months.
[b]Calculated as the total number of such events on complete diary days, divided by the number of complete days.

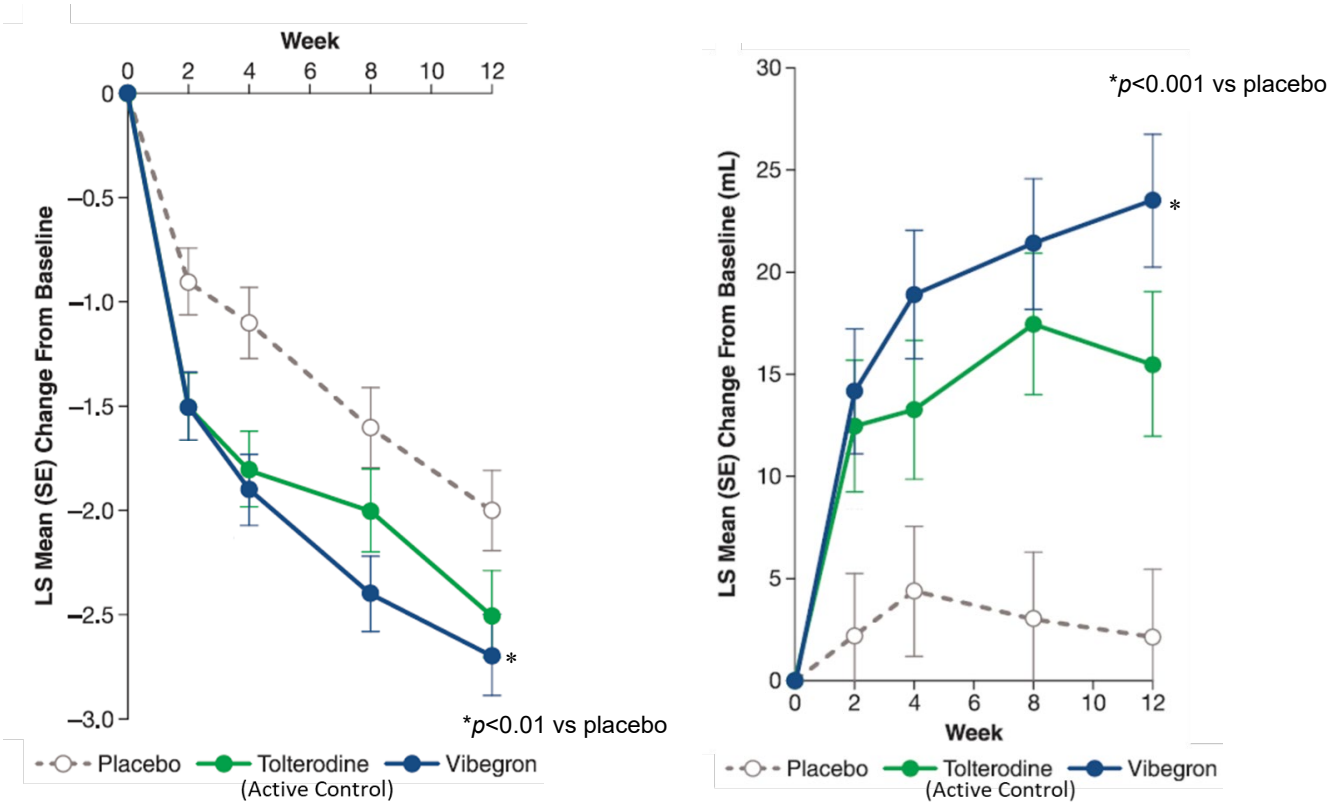
FAS, full analysis set; FAS-I, full analysis set for incontinence; OAB, overactive bladder; SD, standard deviation; UUI, urge urinary incontinence.

Key Secondary Efficacy End Points

At Week 12, the LSM change in baseline daily urgency episode frequency among subjects in the vibegron group (n=492) was -2.7 episodes vs -2.0 among 475 subjects in the placebo group (n=475), a LSM difference of -0.7 (95% CI -1.1, -0.2; p=0.0020) (Figure 2). For the tolterodine (active control) group (n=378), the LSM change was -2.5, a LSM difference of -0.4 from placebo (95% CI -0.9, 0.0; p=0.0648). Efficacy was observed within 2 weeks through week 12.[2]

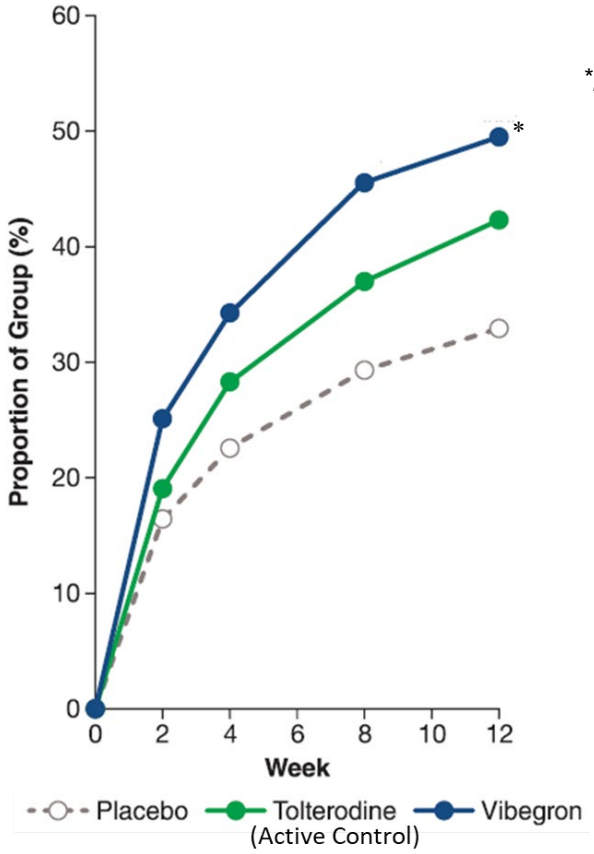
At Week 12, the LSM change in urine volume voided per micturition was 23.5 mL among subjects in the vibegron group (n=490) vs 2.2 mL among subjects in the placebo group (n=478), a LSM difference of 21.2 (95% CI 14.3, 28.1; p<0.0001) (Figure 2). For the tolterodine (active control) group (n=375), the LSM change was 15.5 mL and a LSM difference of 13.3 mL from placebo (95% CI 5.9, 20.7; p<0.001). Efficacy was observed within 2 weeks through week 12.[2]

Figure 2. Change in Urgency Episodes per Day (left) and Volume Voided (mLs) at Week 12 (right)



At Week 12, the proportion of wet OAB cases with ≥75% reduction in baseline daily UUI episodes was 52.4% in the vibegron group vs 36.8% in the placebo group ($p<0.0001$) and 47.6% for the tolterodine (active control) group (Figure 3). The proportion of subjects with ≥75% reduction was larger with vibegron vs placebo group within 2 weeks through week 12. Across all primary and key secondary end points, the numerical results were consistently greater for vibegron vs tolterodine (active control).[2]

Figure 3. Patients Achieving a ≥75% Reduction in UUI Episodes



Safety

Among subjects in the vibegron group, adverse events (AEs) with an incidence ≥2.0% and greater than placebo were headache (4.0% vs 2.4%), nasopharyngitis (2.8% vs 1.7%), diarrhea (2.2% vs 1.1%), nausea (2.2% vs 1.1%), and upper respiratory tract infection (2.0 vs 0.7%).[2]

Among subjects in the tolterodine (active control) group, AEs with an incidence >2.0% and greater 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%), diarrhea (2.1% vs 1.1%).[2]

Nine subjects in the vibegron group (1.7%), six in the placebo group (1.1%) and 14 in the tolterodine (active control) group (3.3%) discontinued the study drug due to AEs.[2]

Laboratory assessments, vital signs and physical examination findings were not associated with any clinically relevant changes from baseline in any treatment group. There were no clinically relevant differences in post-treatment blood pressure between subjects who were hypertensive or not hypertensive at baseline.[2]

Post void residual (PVR) urine volume data were collected via bladder ultrasound at the Run-in Visit and Week 12 Visit. At Week 12, there was no clinically relevant change from baseline in mean PVR urine volume for subjects treated with vibegron compared with placebo (**Table 2**). Treatment with vibegron did not result in increased urinary retention in subjects relative to placebo.[4]

Table 2. Post-Void Residual Urine Volume

Timepoint	Placebo n=540	Vibegron n=545	Tolterodine (active control) n=430
Baseline, n	539	544	430
Mean Urine Volume, mL (SD)	27.1 (31.1)	28.8 (32.5)	27.9 (37.9)
Week 12, n	503	511	400
Mean Change, mL (SD)	2.1 (37.3)	0.4 (38.3)	3.1 (40.9)

In this phase III study, vibegron 75 mg provided statistically significant and 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. Efficacy was observed within 2 weeks through week 12. Vibegron had AE rates comparable with those for placebo, including the incidence of hypertension.[2]

References

1. GEMTESA® [package insert]. Irvine, CA: Urovant Sciences, Inc; 2020
2. Staskin D, Frankel J, Varano S, et al. 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. *J Urol*. 2020;204:316-324. https://www.auajournals.org/doi/10.1097/JU.0000000000000807
3. Staskin D, Frankel J, Varano S, et al. 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. *J Urol*. 2020;204:316-324. Supplementary Table 2. https://www.auajournals.org/action/downloadSupplement?doi=10.1097%2FJU.0000000000000807&file=Supplementary_table2.pdf
4. Data on file (2019) Urovant Sciences. Clinical Study Report. An International Phase 3, Randomized, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder.