UROVANT SCIENCES

Vibegron: Health-Related Quality of Life

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. Please see accompanying full Prescribing Information.

Summary

- Validated patient-reported outcome (PROs) questionnaires serve as important and clinically relevant endpoints in the study of patients with OAB[1]
- Overactive Bladder Questionnaire Long Form (OAB-q LF) is a 33-item patient-administered, disease-specific PRO, divided into two scales: Health-Related Quality of Life (HRQL) and Symptom Bother[2]
- The efficacy of vibegron, a selective oral beta-3 adrenergic agonist, has been assessed in phase 2 and 3 trials[2]
- EMPOWUR was an international Phase 3, randomized, double-blind, placebo, and active control study conducted to evaluate the safety and efficacy of vibegron in patients with symptoms of OAB (N=1518)[3]
- Quality of Life (QoL) were secondary and exploratory endpoints in EMPOWUR; OAB-q LF was the instrument used to assess QoL[2,3]
- In the EMPOWUR study, treatment with vibegron resulted in a greater least square mean change from baseline at week 12 compared to placebo or tolterodine on all four OAB-q HRQL subscales and the bother scale[2]
- At week 12, vibegron treated subjects experienced statistically significant improvements on the OAB-q symptom bother scale, HRQL total score, and all HRQL subscales except social interaction when compared to placebo[2]

Patient-Reported Outcomes

Patients with OAB experience urinary frequency and urgency symptoms that can occur with incontinence (OAB wet) or without incontinence (OAB dry). Studies have shown that OAB symptoms can negatively impact the quality of life (QoL) of patients with OAB.[3] In the EpiLUTS survey that included 20,000 participants, respondents with OAB and bothersome symptoms reported increased anxiety and depression in addition to worse HRQL, compared to those who responded to the survey with no or minimal symptoms.[2] Validated patient-reported outcome questionnaires (PROs) serve as important and clinically relevant endpoints in the study of patients with OAB. They are used to capture patients' perception of their symptoms and health-related quality of life (HRQL).[2] The Overactive Bladder Questionnaire (OAB-q) was a key secondary and exploratory endpoint in EMPOWUR, an international Phase 3, randomized, double-blind, placebo and active control study to evaluate the safety and efficacy of vibegron in patients with symptoms of OAB.[2] The OAB-q Long Form (OAB-q LF) is a 33-item patient-administered, disease-specific questionnaire divided into an HRQL scale and a symptom bother scale. The HRQL scale consists of 25-items, each scored from 1-6 with higher scores indicating

better QoL, divided into four subscales: coping, concern, sleep, and social interaction.[2] The symptom bother scale contains 8-items scored from 1-6, with higher scores indicating more severe symptoms. In the EMPOWUR study, patients completed the OAB-q LF at baseline and the end-of-study at week 12 study, using a 1-week recall period.[2]

EMPOWUR

Study design

EMPOWUR was an international Phase 3, randomized, double-blind, placebo, and active control study conducted to evaluate the safety and efficacy of vibegron in patients with symptoms of OAB. Patients were required to be at least 18 years of age with a history of OAB to be eligible for study participation. Patients with OAB wet and dry were included in the study; however, enrollment was limited to 25% for patients with OAB dry.[3] Following a 1-to-5-week screening period, a 28-day washout period, and a 2-week single-blind (patient) placebo run-in period, eligible patients were randomized into a 12-week treatment period followed by a 4-week follow-up safety evaluation. Patients were randomized into one of three treatment groups, vibegron 75 mg, placebo, or 4 mg tolterodine ER (active control); all treatments were self-administered, once daily every morning.[3]

The study was powdered to detect a treatment difference between vibegron and placebo; all other efficacy comparisons between study groups were considered supportive and given nominal p values.[3]

Co-primary endpoints

The two co-primary endpoints were change from baseline to week 12 in the average daily number of micturitions and change from baseline to week 12 in the average daily number of urge urinary incontinence (UUI) episodes.[3]

Secondary and Exploratory QoL endpoints

Key secondary efficacy endpoints included change from baseline to week 12 in the average number of daily urgency episodes, the coping subscale on the OAB-q, the percentage of OAB wet patients with ≥75% reduction in daily UUI episode, the average number of daily total incontinence episodes and change in average volume voided per micturition.[3] Additional secondary and exploratory QoL endpoints at week 12 included changes in the OAB-q subscales scores related to concern, sleep, social interaction, HRQL total score, and symptom bother.[2]

Results

Co-primary endpoints

A total of 1,518 patients were randomized into the study. Patient baseline characteristics were well balanced across the three treatment groups.[3] Approximately 85% of subjects were women and 15% men with a mean age of 60 years; of these, 77% had a diagnosis of OAB wet and 23% OAB dry.[2] At the end of the study, at week 12, the change in the average number of daily micturitions in the vibegron group (n=492) was -1.8 episodes per day, compared to placebo

(n=475) -1.3 episodes per day, resulting in a statistically significant least square (LS) mean difference of -0.5 (95% CI -0.8, -0.2; *p*<0.0010).[3] For the co-primary endpoint of the average daily number of UUI episodes, statistically significant reductions from baseline were observed at week 12 in the vibegron group (adjusted mean – 2 episodes per day) compared to the placebo group (adjusted mean -1.4 episodes per day), resulting in a statistically significant LS mean difference of -0.6 (95%CI -0.9, -0.3; p<0.0001). Efficacy was observed as early as week 2 (exploratory endpoint).[3]

Secondary and exploratory OAB-q LF HRQL and symptom bother endpoints

Patients in the vibegron treatment group experienced greater least square mean changes from baseline at week 12 than placebo or active control on all four OAB-q HRQL subscales and the symptom bother scale.[2] At week 12, improvements in the vibegron treated group were statistically greater than placebo for the symptom bother scale, HRQL total score, and all HRQL subscales except social interaction [Table 1].[2] Numerically greater improvements in OAB-q scores from baseline to week 12 were observed in the vibegron treated group compared to active control treated group; however, no direct statistical comparison was performed between the two treatment groups.[2]

Table 1: Overactive Bladder Questionnaire (OAB-q) Mean Change from Baseline at Week 12

OAB-q LS mean change*	Placebo	Vibegron	Active Control	Vibegron vs. Placebo	Active Control vs. Placebo
HRQL Coping Subscale	12.9 (1.3)	16.5 (1.3)	16.0 (1.4)	*p*<0.01	*p*<0.05
HRQL Concern Subscale	10.3 (1.3)	15.3 (1.2)	14.8 (1.3)	*p*<0.001	*p*<0.001
HRQL Sleep Subscale	10.4 (1.4)	14.8 (1.3)	13.0 (1.4)	*p*<0.001	NS
HRQL Social Interaction Subscale	8.8 (1.0)	10.2(1.0)	9.3 (1.0)	NS	NS
HRQL Total Scale	10.8 (1.1)	14.6 (1.1)	13.7 (1.2)	*p*<0.001	*p*<0.05
Symptom Bother Scale	-12.8 (1.3)	-19.6 (1.2)	-17.4 (1.3)	*p*<0.0001	*p*<0.001

*Results represent least square mean changes at week 12 from baseline with missing item imputation. Missing imputation rule: the mean scale of non-missing items is used if <50% of the scale items are missing; if ≥50% of the items are missing, the scale score is set to missing.

A post hoc analysis was performed to calculate the percentage of patients considered a responder for the OAB-q scale and subscales scores at week 12. Patients were classified as responders for the OAB-q scale if they were determined to have achieved at least a minimally

important difference of ≥ 10-point from baseline.[2] At week 12, compared to placebo, vibegron treated patients were significantly more likely to be classified as a responder in the coping score (odds ratio [OR], 1.44 [95% CI, 1.09-1.90]: $p<0.05$) and symptom bother score (OR, 1.89 [95% CI, 1.43-2.50]: $p<0.0001$). The OR [95% CI] for vibegron versus placebo was more favorable than for active control versus placebo at week 12 for sleep (1.20 [0.91-1.59] vs 1.10 [0.82-1.47]), social interaction (1.32 [0.94-1.85] vs 1.21 [0.84-1.74]), HRQL total (1.32 [0.99-1.75] vs 1.26 [0.93-1.70]), and symptom bother (1.89 [1.43-2.50] vs 1.64 [1.22-2.20]).[2]

Safety and Tolerability

The protocol defined adverse events (AEs) of clinical interest included potential major cardiac or cerebrovascular events, new-onset or worsened hypertension, increased blood pressure, AEs consistent with orthostatic hypotension, cystitis, or urinary tract infections, and elevated liver enzymes leading to study drug interruption or discontinuation. Clinical laboratory assessments, vital signs, and physical exam were included in the safety measures.[3]

The following AEs of clinical interest were reported at a similar rate in the vibegron and placebo groups; hypertension, blood pressure increased, urinary tract infection, and urinary retention. There were no reports of tachycardia. Dry mouth was less common with vibegron (1.7%) than with active control (6.5%) but more common than in placebo (0.9%).[3]

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

Safety Population, n (%)	Placebo (n=540)	Vibegron (n=545)	Active Control (n=430)
Patients with ≥1 serious TEAE	6 (1.1)	8 (1.5)	10 (2.3)
Discontinuation due to TEAE	6 (1.1)	9 (1.7)	14 (3.3)
TEAEs (vibegron >2% and > placebo			
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)
Selected AEs of clinical interest			
Hypertension	9 (1.7)	9 (1.7)	11 (2.6)
Blood pressure increased	5 (0.9)	4 (0.7)	8 (1.9)
Urinary tract infection	33 (6.1)	27 (5.0)	25 (5.8)
Urinary retention	2 (0.4)	3 (0.6)	3 (0.7)

AE: adverse event; TEAE; treatment-emergent adverse event. Table modified from Table 2 Staskin D et al.J Urol. 2020;204:316-324

References

1. Coyne K, Revicki D, Hunt T, Corey R, Steward W, Bentkover J, Kurth H, Abrams R. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: The OAB-q. Qual Life Res. 2002;11(6):563-574
2. Frankel J, Varano S, Staskin D, Shortino D, Jankowich R, Mudd PN Jr. Vibegron improves quality-of-life measures in patients with overactive bladder: Patient-reported outcomes from the EMPOWUR study. Int J Clin Pract. 2020 Dec 17:e13937. doi: 10.1111/ijcp.13937. https://onlinelibrary.wiley.com/doi/10.1111/ijcp.13937
3. Staskin D, Frankel J, Varano S, Shortino D, Jankowch R, Mudd PR, Jr. Internation 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