Vibegron improves quality-of-life measures in patients with overactive bladder: Patient-reported outcomes from the EMPOWUR study

Jeffrey Frankel | Susann Varano | David Staskin | Denise Shortino | Rachael Jankowich | Paul N. Mudd Jr

Abstract

Background: Quality of life (QOL) can be significantly impacted by symptoms of overactive bladder (OAB). Vibegron is a highly selective $\beta_3$-adrenergic receptor agonist that showed efficacy in treatment of symptoms of OAB in the randomised, double-blind, placebo- and active-controlled phase 3 EMPOWUR trial. Here we report patient-reported QOL outcomes from the EMPOWUR trial.

Methods: Patients were randomly assigned 5:5:4 to receive vibegron 75 mg, placebo or tolterodine 4 mg extended release, respectively, for 12 weeks. Patients completed the OAB questionnaire (OAB-q) at baseline and at week 12 and the patient global impression (PGI) scales for severity, control, frequency and leakage at baseline and at weeks 4, 8 and 12. Change from baseline at week 12 and responder rates (OAB-q: patients achieving a ≥10-point improvement; PGI: patients reporting best possible response) were assessed. Vibegron was compared with placebo, and no comparisons were made between vibegron and tolterodine.

Results: Of the 1518 patients randomised, 1463 (placebo, n = 520; vibegron, n = 526; tolterodine, n = 417) had evaluable data for efficacy measures and were included in the analysis. Mean baseline OAB-q and PGI scores were comparable among treatment groups. At week 12, patients receiving vibegron had greater improvements from baseline in OAB-q subscores of coping, concern, sleep, health-related QOL total and symptom bother ($P < .01$ each) compared with patients receiving placebo; a greater proportion of patients receiving vibegron vs placebo were responders in the OAB-q coping ($P < .05$) and symptom bother scores ($P < .0001$). Compared with placebo, a greater proportion of patients who received vibegron achieved the best response on all PGI end-points at week 12 ($P < .05$ each) and were classified as responders ($P < .05$ each).
1 | INTRODUCTION

An estimated 23% of US adults ≥40 years old experience bothersome symptoms of overactive bladder (OAB), which can significantly affect quality of life (QOL). Symptoms such as urge urinary incontinence (UUI) are associated with substantial personal burden, including reduced health-related QOL (HRQL). Furthermore, patient perception of symptom severity can affect measures of QOL. As measured using the OAB questionnaire (OAB-q), a gold-standard measurement in the field, bothersome symptoms of OAB affect a patient’s mental health. In the EpiLUTS survey that included 20,000 participants, respondents with OAB and bothersome symptoms reported not only worse HRQL but also increased anxiety and depression compared with respondents with no or minimal symptoms. The psychological impact of OAB can extend beyond anxiety and depression; patients with OAB often report significantly more embarrassment and shame and a greater impact on social and sexual relationships compared with individuals without OAB. As OAB affects both physical and psychological health, and in some cases may lack clinically objective markers, effectively capturing the patient’s voice through the OAB-q can allow physicians to optimise patient care.

Goals of treatment for OAB include maximising symptom control and QOL while minimising adverse events (AEs). As such, a patient’s willingness to continue taking their medication is imperative to maximise symptom benefit and subjective measures of QOL, which can further improve treatment adherence and persistence. However, a survey of patients taking OAB medications showed that nearly 50% of respondents who discontinued medication reported the medication not working as expected as the primary reason for discontinuation; further, 21% of respondents reported having side effects (ie, poor tolerability) as a reason for discontinuation.

Vibegron is a novel, highly selective oral β3- adrenergic receptor agonist that has a favourable drug-drug interaction profile. The efficacy of once-daily vibegron for the treatment of OAB has been assessed in phase 2 and 3 trials. EMPOWUR was an international, 12-week placebo- and active-controlled phase 3 trial that evaluated the safety and efficacy of vibegron in patients with symptoms of OAB (N = 1518). Patients treated with vibegron showed significant improvement vs placebo at week 12 in the coprimary end-points of reduction in micturitions (P < .001) and UUI episodes (P < .0001), as well as in key secondary end-points. Onset of efficacy was rapid, with significant differences vs placebo observed by week 2, which were sustained throughout the trial. Because symptom severity has been shown to be correlated with patient-reported QOL, treatment resulting in symptomatic improvement would likely result in concomitant improvement in QOL measures in the EMPOWUR study. Here we present additional secondary and exploratory end-points from EMPOWUR to assess the effect of 12 weeks of treatment with vibegron on patient-reported QOL.

2 | METHODS

2.1 | Study design and patients

Detailed methods of the international, phase 3, randomised, double-blind, placebo- and active-controlled EMPOWUR trial has been previously published. Briefly, adults with OAB were eligible for inclusion if they had wet or dry OAB for ≥3 months before the screening visit. Wet OAB was defined as an average of ≥8 micturitions and ≥1 UUI episodes per day. Dry OAB was defined as an average of ≥8 micturitions, <1 UUI episode and ≥3 urgency episodes per day. Up to 15% of patients enrolled could be men, and up to 25% could have dry OAB. Patients were randomly assigned 5:5:4 to receive vibegron 75 mg, placebo, or tolterodine 4 mg extended release, respectively, once daily for 12 weeks. The EMPOWUR trial was approved by an institutional review board, research ethics board or independent ethics committee before initiation, and all patients provided written informed consent before participating in any study procedures.

Conclusions: In the 12-week EMPOWUR trial, treatment with vibegron was associated with significantly greater and clinically meaningful improvement in OAB-q and PGI scores compared with placebo, consistent with improvements in OAB symptoms. Clinical trial registration: ClinicalTrials.gov identifier number NCT03492281.

What’s known

- Bothersome symptoms of overactive bladder (OAB) negatively impact quality of life (QOL).
- Vibegron is a β3-adrenergic receptor agonist that has been shown to be safe and effective for the treatment of OAB in the phase 3 EMPOWUR trial.

What’s new

- Treatment with vibegron was associated with improved QOL as assessed by the OAB questionnaire and patient global impression scale.
- Consistent with symptomatic improvement, vibegron improves QOL in patients with OAB.
Patients completed the OAB-q long form for a 1-week recall period at baseline and at week 12. The OAB-q is a patient-reported, 33-item, disease-specific and validated instrument that was selected to assess symptom bother and the overall impact of OAB on HRQL. The questionnaire contains an 8-item symptom bother score (items scored from 1 to 6, with higher scores indicating greater symptom severity) and a 25-item HRQL score (items scored from 1 to 6, with higher scores indicating better QOL). The HRQL score includes four subscales: coping, concern, sleep and social interaction.

### TABLE 1 Patient baseline demographics, clinical characteristics and QOL measures (full analysis set)

| Characteristic          | Placebo  | Vibegron | Tolterodine |
|-------------------------|----------|----------|-------------|
|                         | N = 520  | N = 526  | N = 417     |
| Mean (SD) age, y        | 59.9 (13.3) | 60.8 (13.3) | 59.8 (13.2) |
| Men, n (%)              | 75 (14.4) | 77 (14.6) | 65 (15.6)   |
| Wet OAB, n (%)          | 405 (77.9) | 403 (76.6) | 319 (76.5)  |
| Mean (SD) OAB-q score, n| 518      | 524      | 416         |
| Total HRQL              | 63.7 (23.5) | 62.7 (24.9) | 64.5 (22.9) |
| Coping                  | 58.7 (27.1) | 57.6 (28.1) | 59.8 (26.4) |
| Concern                 | 63.5 (25.9) | 61.9 (27.4) | 63.7 (26.0) |
| Sleep                   | 57.1 (26.4) | 58.0 (27.9) | 59.6 (25.2) |
| Social interaction a    | 78.7 (25.0) | 76.8 (26.0) | 78.3 (24.7) |
| Symptom bother          | 50.1 (20.6) | 49.7 (22.0) | 48.0 (20.6) |
| Mean (SD) PGI score, n  | 519      | 525      | 417         |
| PGI-severity            | 3.0 (0.6)  | 3.0 (0.6)  | 3.0 (0.6)   |
| PGI-control             | 3.2 (1.0)  | 3.2 (0.9)  | 3.2 (0.9)   |
| PGI-frequency           | 3.8 (0.8)  | 3.8 (0.8)  | 3.7 (0.9)   |
| PGI-leakage             | 3.3 (0.9)  | 3.4 (0.8)  | 3.3 (0.9)   |
| PGI-change              | 3.6 (1.1)  | 3.6 (1.1)  | 3.5 (1.1)   |

Abbreviations: HRQL, health-related QOL; OAB, overactive bladder; OAB-q, OAB questionnaire; PGI, patient global impression; QOL, quality of life; SD, standard deviation.

As an example, questions asked patients to consider over the past week the severity of their symptoms (severity), control of their symptoms (control), frequency of symptoms (frequency), frequency of urine leakage (leakage) and severity of symptoms compared with the start of the study (change). The key QOL secondary end-point was change from baseline at week 12 in OAB-q coping subscale score. Additional QOL secondary and exploratory end-points were change from baseline at week 12 in OAB-q HRQL total score, subscale scores and symptom bother score and change from baseline at week 12 in PGI scores.

### 2.3 Statistical analysis

Analysis of QOL end-points compared vibegron with placebo. Tolterodine was included as an active control, but no statistical comparisons were made between vibegron and tolterodine. Analyses were performed using the full analysis set, which included all randomised patients who received ≥1 dose of study treatment and had ≥1 evaluable change from baseline micturition measurement. Least squares (LS) mean differences for changes from baseline parameters in each active arm vs placebo (and associated two-sided 95% CIs) were estimated using a mixed model for repeated measures with restricted maximum likelihood estimation, with terms for treatment, visit, sex, region, OAB type, baseline score and visit-by-treatment interaction. To account for missing data, if <50% of the scale or subscale items were missing, the scale was retained as the mean score.
Note: HRQL items were scored from 1 to 6, with higher scores indicating better QOL; increases in scores indicate improvement. Symptom bother items were scored from 1 to 6, with higher scores indicating greater symptom severity; decreases in scores indicate improvement.

If <50% of items were available, the subscore was regarded as missing; if ≥50% of items were available, the subscore included missing items imputed as the average of the remaining non-missing items for the subscore.

Abbreviations: CI, confidence interval; HRQL, health-related QOL; LSMD, least-squares mean difference; OAB, overactive bladder; OAB-q, OAB questionnaire; QOL, quality of life.

Table 2: LSMD in OAB-q scores vs placebo at week 12 (full analysis set)

Table 3: LSMD in PGI scores vs placebo at week 12 (full analysis set)

Note: The PGI is scored from 1 to 4 for severity; 1 to 5 for control, frequency and leakage; and 1 to 7 for change. Lower scores indicate better QOL; decreases in score indicate improvement.

Abbreviations: CI, confidence interval; LSMD, least-squares mean difference; PGI, patient global impression; QOL, quality of life.

Table 2

Table 3

Note: The PGI is scored from 1 to 4 for severity; 1 to 5 for control, frequency and leakage; and 1 to 7 for change. Lower scores indicate better QOL; decreases in score indicate improvement.

Abbreviations: CI, confidence interval; LSMD, least-squares mean difference; PGI, patient global impression; QOL, quality of life.

Table 3

Note: The PGI is scored from 1 to 4 for severity; 1 to 5 for control, frequency and leakage; and 1 to 7 for change. Lower scores indicate better QOL; decreases in score indicate improvement.

Abbreviations: CI, confidence interval; LSMD, least-squares mean difference; PGI, patient global impression; QOL, quality of life.
achieving the best possible response at week 12 were derived from a post hoc analysis using a logistic regression model that included terms for OAB type, sex and baseline response.

3 | RESULTS

3.1 | Patients

Overall, 1518 patients were randomised (placebo, n = 540; vibegron, n = 547; tolterodine, n = 431). Of the randomised patients, 1463 had evaluable data for changes in micturitions and were included in the full analysis set. Patient demographics and clinical characteristics were well balanced across the three treatment groups (Table 1). Overall, mean (SD) age was 60.2 (13.3) years. By trial design, 85% of patients were women, and 77% had wet OAB. Mean baseline OAB-q and PGI scores were also comparable among treatment groups (Table 1).

3.2 | OAB-q measures

Patients receiving vibegron had significantly greater improvement from baseline to week 12 in OAB-q coping subscale score compared with placebo (LS mean [SE] change: 16.5 [1.3] vs 12.9 [1.3], respectively; \( P < .01 \); Figure 1). Patients receiving vibegron also had greater improvement from baseline to week 12 in concern, sleep, HRQL total and symptom bother subscale scores (Figure 1). The between-group difference at week 12 for vibegron vs placebo was significant for five of the six OAB-q measures (coping, concern, sleep, HRQL total, symptom bother; Table 2). Although direct statistical comparisons were not performed, patients treated with vibegron had numerically greater improvement in OAB-q scores from baseline to week 12 compared with tolterodine. At week 12, greater percentages of patients receiving vibegron compared with placebo were classified as responders for the OAB-q coping (61.9% vs 54.4%, respectively), concern (55.7% vs 49.8%), sleep (53.9% vs 51.8%), social interaction (40.6% vs 35.2%), HRQL total (54.1% vs 48.6%) and symptom bother (70.1% vs 58.3%) scores. At week 12, patients treated with vibegron vs placebo were significantly more likely to be classified as responders in the coping score (OR, 1.44 [95% CI, 1.09-1.90]; \( P < .05 \)) and symptom bother score (OR, 1.89 [95% CI, 1.43-2.50]; \( P < .0001 \)). The OR [95% CI] for vibegron vs placebo was more favourable than for tolterodine vs placebo at week 12 for sleep (1.20 [0.91-1.59] vs 1.10 [0.82-1.47], respectively), 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]).

3.3 | PGI measures

LS mean change from baseline at week 12 was significantly improved with vibegron for all PGI end-points compared with placebo (Table 3). Patients treated with vibegron had numerically greater LS mean change from baseline at week 12 compared with tolterodine. A greater proportion of patients who received vibegron reported the most favourable responses on PGI end-points at week 12 compared with placebo (Figure 2). At week 12, patients treated with vibegron vs placebo were significantly more likely to report best response for each PGI end-point; ORs and 95%
CIs for vibegron vs placebo were >1.0 for all PGI end-points. The overall distribution of responses for each PGI measure shifted over time from less favourable to more favourable responses, with significantly greater changes from baseline seen with vibegron vs placebo (Figure 3). The OR [95% CI] for vibegron vs placebo was more favourable than for tolterodine vs placebo for all PGI measures at week 12: severity (2.2 [1.4-3.5] vs 1.4 [0.8-2.3], respectively), control (2.2 [1.5-3.3] vs 1.7 [1.1-2.6]), frequency (2.4 [1.4-4.3] vs 1.7 [0.9-3.3]), leakage (1.6 [1.1-2.4] vs 1.0 [0.6-1.5]) and change (2.2 [1.6-2.9] vs 1.6 [1.1-2.2]).

4 | DISCUSSION

In this analysis of patient-reported outcomes from the EMPOWUR trial, 12 weeks of treatment with once-daily vibegron was associated with significant improvement in subjective QOL outcomes related to OAB, extending results of the coprimary and key secondary end-points in which vibegron significantly improved OAB symptoms compared with placebo.⁷ Consistent with significant and rapid improvements observed on all efficacy parameters,⁷ patients receiving vibegron had significantly greater improvements vs placebo at week 12 for OAB-q coping, concern, sleep and symptom bother subscale scores and HRQL total score. Patients receiving vibegron also had greater improvement in PGI scores vs placebo at week 12, and a significantly higher percentage of patients indicated the best possible response in individual PGI measures, suggesting that they were unaffected or minimally affected by symptoms of OAB. Patients receiving tolterodine also showed significant improvement vs placebo at week 12 for OAB-q coping, concern and symptom bother subscale scores and HRQL total score and for PGI measures, consistent with the results of previous studies.¹⁶-¹⁸
Scores for the OAB-q social interaction subscale were relatively high at baseline across all treatment groups, indicating high patient-perceived QOL with respect to social interaction. It is therefore not surprising that patients receiving vibegron or tolterodine did not show significant differences vs placebo after 12 weeks. These results are in agreement with previous analyses in which the social interaction subscale has shown the smallest effect size compared with the other OAB-q subscales.\textsuperscript{19,20}

Although objective efficacy measures are able to show clear benefit for patient symptoms, it is important to show that symptomatic improvements also translate into improvements in patient-reported QOL. As such, guidance from the International Continence Society recommends assessing QOL measures in addition to symptom measures.\textsuperscript{21} Patient satisfaction with treatment, which can differ among patients owing to intrinsic characteristics or beliefs (ie, that of efficacy and tolerability), can also influence subjective QOL and is an important factor contributing to treatment adherence.\textsuperscript{8} Vibegron has been shown to be safe and well tolerated, with a low incidence of AEs,\textsuperscript{9} which may also improve treatment adherence and be associated with improved QOL.\textsuperscript{22} The 12-week EMPOWER\textsuperscript{\textregistered} study was a relatively short duration to measure long-term treatment adherence and persistence, but subjective measures of QOL may provide insight into a patient’s likelihood of continuing treatment. A 10-point change in OAB-q subscales has been shown to represent a MID\textsuperscript{20} and suggests that patients achieving this change in score perceive greater treatment benefit and potentially greater satisfaction. In this study, responder analysis at week 12 showed that a significantly higher percentage of patients receiving vibegron compared with placebo achieved a MID in OAB-q coping and symptom bother subscale scores.

Despite the QOL end-points being secondary objectives in the EMPOWER trial, validated measures (ie, OAB-q long form for 1-week recall and PGI) were used, and the results were robust in the large patient population. While 12 weeks of treatment with vibegron are generally sufficient to demonstrate clinical efficacy, long-term effects of vibegron on OAB outcomes and QOL measures may be more meaningful. Furthermore, EMPOWER was not designed to assess differences between vibegron and the active control, tolterodine; however, patients receiving vibegron had numerically greater improvements in all OAB-q scores and all PGI scores from baseline to week 12 compared with those receiving tolterodine.

5 CONCLUSION

In the 12-week EMPOWER trial, patients treated with vibegron experienced significantly greater and clinically meaningful improvements compared with placebo in patient-reported QOL measures. Vibegron treatment improves symptomatic efficacy measures as well as QOL measures and should lead to improved treatment adherence and persistence. Vibegron may represent an important new therapy to address a high unmet medical need for patients with OAB.
11. Mitcheson HD, Samanta S, Muldowney K, et al. 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. *Eur Urol*. 2019;75:274-282.

12. Yoshida M, Takeda M, Gotoh M, Nagai S, Kurose T. Vibegron, a novel potent and selective β3-adrenoreceptor agonist, for the treatment of patients with overactive bladder: a randomized, double-blind, placebo-controlled phase 3 study. *Eur Urol*. 2018;73:783-790.

13. Homma Y, Gotoh M. Symptom severity and patient perceptions in overactive bladder: how are they related? *BJU Int*. 2009;104:968-972.

14. Coyne KS, Gelhorn H, Thompson C, Kopp ZS, Guan Z. The psychometric validation of a 1-week recall period for the OAB-q. *Int Urogynecol J*. 2011;22:1555-1563.

15. Tincello DG, Owen RK, Slack MC, Abrams KR. Validation of the Patient Global Impression scales for use in detrusor overactivity: secondary analysis of the RELAX study. *BJOG*. 2013;120:212-216.

16. Kelleher CJ, Kreder KJ, Pleil AM, Burgess SM, Reese PR. Long-term health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. *Am J Manage Care*. 2002;8:S616-S630.

17. Kelleher CJ, Reese PR, Pleil AM, Okano GJ. Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. *Am J Manage Care*. 2002;8:S608-S615.

18. Roberts R, Bavendam T, Glasser DB, Carlsson M, Eyland N, Elinoff V. Tolterodine extended release improves patient-reported outcomes in overactive bladder: Results from the IMPACT trial. *Int J Clin Pract*. 2006;60:752-758.

19. Coyne KS, Matza LS, Thompson CL. The responsiveness of the Overactive Bladder Questionnaire (OAB-q). *Qual Life Res*. 2005;14:849-855.

20. Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V. Determining the importance of change in the overactive bladder questionnaire. *J Urol*. 2006;176:627-632.

21. Mattiasson A, Djurhuus JC, Fonda D, Lose G, Nordling J, Stöhrer M. Standardization of outcome studies in patients with lower urinary tract dysfunction: a report on general principles from the Standardisation Committee of the International Continence Society. *Neurourol Urodyn*. 1998;17:249-253.

22. Kim A, Lee KS, Jung R, et al. Health related quality of life in patients with side-effects after antimuscarinic treatment for overactive bladder. *Low Urin Tract Symptoms*. 2017;9:171-175.

How to cite this article: 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 EMPOWER study. *Int J Clin Pract*. 2021;75:e13937. https://doi.org/10.1111/ijcp.13937