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Vibegron, a Novel Potent and Selective β_3-Adrenoreceptor Agonist, for the Treatment of Patients with Overactive Bladder: A Randomized, Double-blind, Placebo-controlled Phase 3 Study

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Abstract

Background: Vibegron is a novel, potent, and selective β_3-adrenoreceptor agonist for the treatment of patients with overactive bladder (OAB).
Objective: To evaluate the efficacy and safety of vibegron versus placebo in Japanese OAB patients.
Design, setting, and participants: Patients with OAB entered a 2-wk placebo run-in phase. Once eligibility ($\geq$8 micturition/d and either $\geq$1 urgency episodes/d or $\geq$1 urgency incontinence episodes/d) was confirmed, patients entered a 12-wk double-blind treatment phase. The anticholinergic imidafenacin was used as an active reference.
Intervention: A total of 1232 patients were randomly assigned to one of the four 12-wk treatment groups: vibegron (50 mg or 100 mg once daily), placebo, or imidafenacin (0.1 mg twice daily).
Outcome measurements and statistical analysis: The primary endpoint was change in the mean number of micturitions/d at wk 12 from baseline. The secondary endpoints were changes from baselines in OAB symptom variables (daily episodes of urgency, urgency incontinence, incontinence, and nocturia, and voided volume/micturition). Quality of life (QoL) and safety were assessed. A constrained longitudinal data analysis model was used for analysis of efficacy.
Results and limitations: Patients taking vibegron 50 mg and 100 mg orally for 12 wk had significant improvements over the placebo in the primary and secondary endpoints. The proportions of patients with normalization of micturition, resolution of urgency, urgency incontinence, and incontinence were significantly greater than placebo. Vibegron significantly improved QoL, with high patient satisfaction. Incidences of drug-related adverse events with vibegron 50 mg and 100 mg were 7.6%, 5.4%, similar to placebo (5.1%), and less than imidafenacin (10.3%). Treatment was for just 12 wk and a long-term study is needed.
Conclusions: The 12-wk treatment with vibegron is effective and well tolerated in patients with OAB.
Patient summary: This randomized study demonstrated that vibegron is clinically useful for treatment of patients with OAB.
Trial registration JapicCTI-152936. http://www.clinicaltrials.jp/user/cteDetail.jsp.

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1. Introduction

Overactive bladder (OAB) is a symptom complex characterized by urgency, usually with frequency and nocturia, with or without urgency incontinence, in the absence of any other pathology [1]. OAB is a common chronic disease and the prevalence in adults is 10–20% in Japan and Western countries [2–4]. The condition of OAB has a significant negative impact on the quality of life (QoL) of patients [5,6]. The mainstay of pharmacotherapy over the past several decades has been oral anticholinergics [7]. However, many patients discontinue long-term anticholinergic therapy because of limited efficacy and undesirable class-related adverse events (AEs) [8,9]. Therefore, there remains a clear medical need to develop a novel drug with an alternative action mechanism. The findings that the human bladder contains a high level of β_3-adrenergic receptor (AR) messenger RNA and that the agonist at this receptor relaxes detrusor smooth muscle led to the accelerated development of β_3-AR agonists as a treatment target in OAB [10–12]. Mirabegron is the first approved β_3-AR agonist for the treatment of OAB and the only class of compounds that is currently used in clinical practice world-wide [13].

Vibegron is a novel, potent, and selective β_3-AR agonist and shows pharmacological activity in vitro and in vivo [14,15]. A phase 2b randomized, double-blind, placebo- and tolterodine-controlled, clinical study demonstrated that vibegron was effective and well tolerated in a total of 1395 patients with OAB (NCT01314872). The objective of this phase 3 study was to evaluate the efficacy and safety of vibegron 50 mg and 100 mg when given orally for 12 wk in Japanese patients with OAB.

2. Patients and methods

2.1. Study design and patients

This was a multicenter, randomized, four-arm, parallel-group, placebo-controlled phase 3 study in patients with OAB. Imidafenacin, an anticholinergic mainly used in Asia, was used as an active reference. The study was conducted at 109 sites in Japan from July 2015 to June 2016. This study consisted of a single-blind, placebo run-in phase and a double-blind treatment phase (Supplementary Fig. 1). Patients with OAB symptoms for ≥6 mo who met the eligibility criteria (Supplementary Table 1) entered a 2-wk placebo run-in phase. During this phase, patients received two tablets of vibegron placebo and one tablet of imidafenacin placebo in the morning and one tablet of imidafenacin placebo in the evening. Once eligibility was confirmed at the end of the run-in phase, patients were randomly assigned in a 3.3:3.3:3.3:1 ratio to one of the following four treatment groups: vibegron (50 mg or 100 mg once daily), placebo, or imidafenacin (0.1 mg twice daily), with adjustment for sex, prior treatment for OAB (use/no use of anticholinergics and β_3-AR agonist), OAB wet and dry, and baseline mean micturitions. OAB wet was defined as patients with one or more mean urgency incontinence/d at baseline and OAB dry was defined as patients with less than one mean urgency incontinence/d at baseline. The assigned study drug was administered orally after a meal for 12 wk. Blinding was carried out using the double-dummy method.

The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice Guidelines, and was approved by the institutional review board at each study site. All patients gave written informed consent before initiation of any study-specific procedures.

2.2. Efficacy and safety assessments

For assessment of efficacy, patients were asked to complete a 3-d micturition diary before each scheduled visit. They also completed the King's Health Questionnaire (KHQ) [16] at wk 0 and wk 12. Patients' satisfaction was assessed at the end of treatment using a self-administered Patient Global Impression (PGI) [17]. Patient satisfaction levels were defined as *satisfied* consisting of very much improved, much improved, and minimally improved, and *very much satisfied* consisting of very much improved and much improved.

The primary endpoint was a change in the mean micturitions/d at wk 12 from baseline. The secondary endpoints were changes from baselines to each visit in daily mean micturitions, urgency episodes, urgency incontinence episodes, incontinence episodes, nocturia episodes, and voided volume/micturition. The proportion of patients with normalization of micturition (<8 micturition/d) and nocturia (<1 nocturia episode/d), and resolution of urgency, urgency incontinence, and incontinence were assessed at each visit. Resolution was defined as their presence at baseline but not at the endpoint. QoL and patients' satisfaction were also assessed. Safety was assessed according to AEs, clinical tests, postvoided residuals, vital signs, and 12-lead electrocardiogram (ECG).

2.3. Statistical analysis

Sample size was established based on the results of the mean and the standard deviation of the change in the mean micturitions/d in the phase 2b study. A sample size of 192 patients/group provided 90% power to demonstrate the superiority of vibegron over placebo with a two-sided significance level of 5%. Similarly, with respect to changes in the secondary endpoints, the number of patients required per group to demonstrate the superiority over placebo in terms of urgency and urgency incontinence were 284 and 170, respectively. Therefore, this study planned to enroll 330 patients/group, taking into account patient dropout. The number of patients in the imidafenacin group was set to 100 as an active reference without statistical testing for noninferiority of efficacy and safety.

Safety analysis was performed for patients in the safety analysis set (SAF) and efficacy was analyzed for the full analysis set (FAS) primarily, and secondarily in the per protocol set (PPS). The SAF consisted of randomized patients who took ≥1 dose of the study drug and had a safety measurement. The FAS was included in the SAF patients, who had at least an efficacy measurement after the first treatment. The PPS was defined as the subset of patients in the FAS who met all the eligibility criteria without prohibited concomitant drugs/therapies, whose exposure duration of the study drug was ≥42 d, and who took ≥75% of the scheduled study drugs.

The least squares mean (LS mean) and two-sided 95% confidence interval of changes in the efficacy variables from baseline to time of assessment in each group were calculated using a constrained longitudinal data analysis model including the adjustment factors except baseline mean micturitions [18]. For superiority of vibegron over placebo, differences in the primary and secondary efficacy variables on comparison of the vibegron and placebo groups were compared using the constrained longitudinal data analysis model. Similarly, changes in the KHQ domain scores from baseline were analyzed. The proportion of normalization/resolution of OAB symptoms in the vibegron and placebo groups were compared using a chi-square test. All statistical tests used a significance level of 0.05 and were two-sided. AEs were coded using the Medical Dictionary for Regulatory Activities Japanese Edition version 17.1. All analyses were performed using SAS software version 9.4 for Windows (SAS Institute, Cary, NC, USA).

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