STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: 213006

Drug Name: Vibegron

Indication(s): Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency

Applicant: Urovant Sciences GmbH

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1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking approval of vibegron 75 mg for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. To support this claim, the safety and efficacy data from a phase 3 study (3003) along with its extension study (3004) were submitted. The primary objective of this review is to evaluate from a statistical perspective if the submitted information supports this claim.

Study 3003 was a multinational, multi-center, double-blind, randomized, parallel group, placebo- and active (tolterodine)-controlled phase 3 study with a 12-week treatment period. Study 3004 was an extension study with eligible U.S patients who completed study 3003 to evaluate the long-term safety and efficacy of vibegron.

In both studies, efficacy data were collected from a patient-completed event and volume diary and patient-completed questionnaires. Throughout each study, patients filled out the patient voiding diary for 7 days prior to the run-in, baseline, and clinical visits. Patients filled out the volume portion of the diary (urine volume diary) for 1 day (chosen by the subject) of the 7 diary days completed prior to each visit.

For study 3003, the co-primary efficacy endpoints were
- Change from baseline (CFB) at Week 12 in average number of micturitions per 24 hours in all OAB patients
- CFB at Week 12 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients.

The selected secondary efficacy endpoints proposed for hypothesis testing were
- CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients
- Percent of OAB Wet patients with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12
- Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12
- Percent of all OAB patients with at least a 50% reduction from baseline in urgency episodes per 24 hours at Week 12
- CFB at Week 12 in average number of total incontinence episodes over 24 hours in OAB Wet patients
- CFB at Week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB patients
- CFB at Week 12 in average volume voided per micturition in all OAB patients.

For the extension study 3004, safety evaluation was the primary objective and the efficacy evaluation was secondary. The co-primary efficacy endpoints in study 3003 were also evaluated at Week 52 for descriptive purpose only.
The Applicant adhered to the statistical methods for the co-primary and secondary endpoints as specified in the protocol and statistical analysis plan. The Applicant identified that site 10-156 and site 27-105 in study 3003 had potential data anomalies and conducted sensitivity analysis of the co-primary efficacy endpoints excluding the data from the two sites. The data from study 3003 demonstrated that vibegron 75 mg daily had statistically significant improvement in the pre-specified co-primary and selected secondary efficacy endpoints compared with placebo.

From a statistical perspective, vibegron 75 mg is effective in treating overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.
2 INTRODUCTION

2.1 Overview

The Applicant, Urovant Sciences GmbH, seeks approval of vibegron 75 mg once daily (oral) for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency. According to the Applicant, vibegron is a selective agonist for human beta 3-adrenoceptor (beta 3-AR).

The statistical review for this NDA is based on the study RVT-901-3003 (refer as 3003) and its extension study RVT-901-3004 (refer as 3004), which is briefly summarized in Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase and Design</th>
<th>Treatment Period</th>
<th>Follow-up Period</th>
<th># of Patients per Arm</th>
<th>Study Population</th>
</tr>
</thead>
</table>
| 3003  | Multinational multicenter, Phase 3, randomized, double blind, parallel group, placebo and active-controlled | 12 weeks | 4 weeks | Randomized: Placebo: 540 Vibegron 75 mg: 547 Tolterodine SR 4mg: 431 | • ≥18 years of age  
• Had symptoms of overactive bladder for at least 3 months  
• ≥8 micturitions per Diary day  
• For OAB-dry patients: An average of ≥ 3.0 urgency episodes per Diary Day; and An average of < 1.0 UUI episodes per Diary Day; and  
• For OAB-wet Patients: An average of ≥ 1.0 UUI episodes per Diary Day;  
• If stress urinary incontinence was present, the total number of UUI episodes must have been greater than the total number of stress urinary incontinence episodes from the previous visit diary. |
| 3004  | Extension study of 3003 US, multicenter, Phase 3, randomized, double blind parallel group, active-controlled | 40 weeks | 4 weeks | Randomized: Vibegron 75 mg: 274 Tolterodine SR 4mg: 232 | • Had completed participation in Study 3003.  
• Had demonstrated >80% compliance with self-administration of study treatment in Study 3003  
• Had completed a minimum of 4 Complete Diary Days for Study 3003 Week 12. |

Source: Statistical reviewer’s summary from study protocols.

Vibegron’s efficacy and safety were initially evaluated in two double-blind, placebo-controlled efficacy/safety clinical studies (phase 2B study 008 and phase 3 study 301) and their associated long-term extension studies evaluating treatment for up to 52 weeks. These studies focused primarily on doses of 50 and 100 mg (not the to be marketed dose in U.S.), and the primary efficacy was evaluated at Week 8 in Study 008 (not at Week 12 as FDA required), and the study population of study 301 consisted all Japanese patients (not representative for U.S. patient population). Therefore, these two studies are considered as supportive information for the current NDA application and not covered by the current review.
2.2 Data Sources

The study documents, data and additional information were submitted electronically. These items are located in the Electronic Document Room at \cdsesub1\evsprod\NDA213006, under the submissions dated on 12/25/2019 and 3/19/2020.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant submitted both the tabulation data and analysis data for the two studies. The statistical analysis programs were submitted per reviewer’s request. The statistical analyses of efficacy endpoints in each study were carried out following the pre-specified statistical analysis plan.

The Applicant identified that site 10-156 and site 27-105 in study 3003 had potential data anomalies including multiple patients having potential similar handwriting in the diaries and data discrepancies. In addition, a high number of samples containing levels of drug below the limit of quantification at site 10-156 was revealed by PK analysis after database lock. Post-hoc sensitivity analysis excluding these two sites were performed for efficacy evaluation.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.2 Study Design

Study 3003

Study 3003 was a multinational, phase 3, randomized, double-blind, placebo- and active (tolterodine)-controlled, multicenter study to evaluate the safety and efficacy of vibegron 75 mg in patients with symptoms of OAB. The study had a total of 199 sites across 6 countries - United States (176), Canada (7), Poland (6), Hungary (5), Latvia (3), and Lithuania (2).

This study consisted of a screening period (1 to 5 weeks), a single-blind placebo run-in period (2 weeks), a randomized, double-blind treatment period (12 weeks), and a safety follow-up period (4 weeks; for patients who did not enroll in the optional extension study). Patients who completed the Week 12 visit may have been eligible to enroll in the 40-week double-blind extension study 3004 until enrollment of approximately 500 patients into that extension study was achieved (506 were actually enrolled in the extension study). Patients who did not enroll into the optional extension study had a follow-up visit approximately 28 days after the patient’s last dose of study treatment (i.e., at Week 16 for patients who completed the Week 12 Visit, or approximately 4 weeks after withdrawal for patients who discontinued the study early).

Eligible patients were randomized 5:5:4 to one of three treatment groups: vibegron 75 mg, placebo, or tolterodine extended-release (ER) 4 mg, all administered once daily for 12 weeks during the treatment period. Between the baseline and Week 12 visits, patients had study assessments at Week 4 and Week 8. A schematic of the study design is shown as Figure 1.
Study 3004 was a multicenter, phase 3, randomized, double-blind, active (tolterodine)-controlled, 40-week extension study. The primary objective for study 3004 was to evaluate the safety of vibegron 75 mg in patients who had completed study 3003, and efficacy evaluation was the secondary objective. In this extension study, all patients who had been randomized in study 3003 to receive either vibegron 75 mg or tolterodine ER 4 mg continued their same treatment once daily in a blinded fashion for an additional 40 weeks; patients who had been randomized in study 3003 to the placebo group were randomized 1:1 to receive blinded study treatment of vibegron 75 mg or tolterodine ER 4 mg once daily. Thus, through participation in both study 3003 and study 3004 (extension), patients originally randomized to vibegron or tolterodine received 52 weeks total of vibegron or tolterodine treatment, and patients originally randomized to placebo received 40 weeks total of vibegron or tolterodine treatment. This study consisted of a randomized double-blind treatment period (40 weeks), and a safety follow-up period (4 weeks) after the patient’s last dose of study treatment. A schematic of the study design is shown as Figure 2.
### 3.2.2.1 Primary/Key Secondary Efficacy Endpoints

**Study 3003**

Patients were instructed to complete the 7-day voiding diary before each visit in the run-in and treatment periods. The voiding diary recorded the frequency of daily OAB symptoms including all micturitions, urgency, incontinence, and main reason for incontinence by selecting the respective box for each symptom occurring during a given day and night.

A “Diary Day” was defined as the time between when the patient got up for the day each morning (i.e., the time the patient got up for the day yesterday to the time the patient got up for the day today; approximately a 24-hour period).

A “Complete Diary Day” was defined as a Diary Day for which the patient indicated that they had recorded all urinations and any leakages that occurred during that Diary Day. Specifically, on the eDiary the patient responded “Yes” to the corresponding item in the Begin Day Questionnaire to indicate that their data were complete for the preceding Diary Day. On the paper Patient Voiding Diary, the patient checked “Yes” in response to the question “Did you record each time you urinated or leaked during this diary day?”

If a patient completed more than the required 7 days of entry in the Diary, only “Complete” Diary Days within 10 days prior to the current visit were used to calculate eligibility.

The co-primary efficacy endpoints, based on the 7-day micturitions diary were defined as follows,

- Change from baseline (CFB) at Week 12 in average number of micturitions per 24 hours in all OAB patients;
- CFB at Week 12 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients.
The number of micturitions was defined as the number of times a patient voided in the toilet recorded on the voiding diary. Average daily micturitions were calculated as the total number of micturitions that occurred on a complete diary day divided by the number of complete diary days in the voiding diary.

The number of UUI episodes was defined as the number of times a patient checked that they had "urge" as the main reason for the leakage, regardless of whether more than one main reason for leakage in addition to “urge” was checked. Average daily UUI episodes at each study visit was calculated in the same manner as described above for the micturition endpoint. The UUI episodes endpoint was analyzed only in OAB Wet patients.

The Applicant’s also defined the following secondary efficacy endpoints for hypothesis testing with multiplicity control of type I error:

- CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients
- Percent of OAB Wet patients with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12
- Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12 (i.e., percent of OAB Wet patients with zero UUI episodes at Week 12)
- Percent of all OAB patients with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 12
- CFB at Week 12 in average number of total incontinence episodes over 24 hours in OAB wet patients.
- CFB at Week 12 in Coping Score from the OAB-q LF (1-week recall) in all OAB patients
- CFB at Week 12 in average volume voided per micturition in all OAB patients

**Study 3004**

The efficacy endpoints include

- Change from baseline (CFB) at Week 52 in average number of micturitions per 24 hours in all OAB patients
- CFB at Week 52 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients
- CFB at Week 52 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients
- CFB at Week 52 in average number of total urinary incontinence episodes over 24 hours in OAB Wet patients

The efficacy analyses are for descriptive purposes only.

**3.2.2.1 Multiplicity Control Approach**

**Study 3003**

Both co-primary endpoints needed to be significant at the 0.05 level in order to test the selected secondary endpoints. If statistical significance was found at the 0.05 level for both co-primary endpoints, each secondary endpoint would be tested sequentially in the order given above. If statistical significance at the 0.05 level was achieved at all previous secondary endpoints, the next sequential secondary endpoint would be tested. Once a secondary endpoint was found to be insignificant (i.e., p-value ≥ 0.05), the testing procedure would stop.
3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Study 3003

The disposition of study patients is summarized by treatment groups in Table 2. In study 3003, a total of 1518 patients were randomized to three treatment groups and the study discontinuation rate was 9.6%, ranging from 8.2% to 10.7% across the treatment groups. The most common reasons for discontinuation from the study were withdrawal of consent, lost to follow-up and adverse events.

Table 2: Summary of Subject Disposition – Study 3003

<table>
<thead>
<tr>
<th></th>
<th>Placebo 540</th>
<th>Vibegron 75 mg 547</th>
<th>Tolterodine ER 4 mg 431</th>
<th>Overall 1518</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>540 (100)</td>
<td>547 (100)</td>
<td>431 (100)</td>
<td>1518 (100)</td>
</tr>
<tr>
<td>Took at least one dose of double-blind medication</td>
<td>540 (100)</td>
<td>545 (99.6)</td>
<td>430 (99.8)</td>
<td>1515 (99.8)</td>
</tr>
<tr>
<td>Completed the study</td>
<td>486 (90.0)</td>
<td>502 (91.8)</td>
<td>385 (89.3)</td>
<td>1373 (90.4)</td>
</tr>
<tr>
<td>Discontinued from the study</td>
<td>54 (10.0)</td>
<td>45 (8.2)</td>
<td>46 (10.7)</td>
<td>145 (9.6)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>21 (3.9)</td>
<td>14 (2.6)</td>
<td>13 (3.0)</td>
<td>48 (3.2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>14 (2.6)</td>
<td>15 (2.7)</td>
<td>10 (2.3)</td>
<td>39 (2.6)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6 (1.1)</td>
<td>8 (1.5)</td>
<td>13 (3.0)</td>
<td>27 (1.8)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.5)</td>
<td>6 (1.1)</td>
<td>3 (0.7)</td>
<td>17 (1.1)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>3 (0.6)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Subject withdrawn due to PI</td>
<td>1 (0.2)</td>
<td>0</td>
<td>3 (0.7)</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>0</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Subject withdrawn due to Sponsor</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

Reference ID: Table 15, study 3003 report.

For primary efficacy evaluation, the Applicant pre-defined the following analyses datasets in study 3003:

- Full Analysis Set (FAS): all randomized OAB patients who took at least one dose of double-blind study treatment and had at least one evaluable change from baseline micturition measurement;
- Full Analysis Set for Incontinence (FAS-I): all randomized OAB Wet patients who took at least one dose of double-blind study treatment and had at least one evaluable change from baseline UUI measurement;
- Per-protocol Set (PPS): FAS excluding patients with important deviations from the protocol that may substantially affect the results of the primary efficacy endpoints
- Per-Protocol Set for Incontinence (PPS-I): FAS-I excluding patients with important deviations from the protocol that may substantially affect the results of the primary efficacy endpoints

The numbers of patients in the defined efficacy analysis sets are presented in Table 3.
### Table 3: Summary of Efficacy Analysis Sets – Study 3003

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vibegron 75 mg</th>
<th>Tolterodine ER 4 mg</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 540&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N = 547&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N = 431&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N = 1518&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Full Analysis Set (FAS)</td>
<td>520 (96.3)</td>
<td>526 (96.2)</td>
<td>417 (96.8)</td>
<td>1463 (96.4)</td>
</tr>
<tr>
<td>Full Analysis Set for Incontinence (FAS-I)</td>
<td>405 (75.0)</td>
<td>403 (73.7)</td>
<td>319 (74.0)</td>
<td>1127 (74.2)</td>
</tr>
<tr>
<td>Per-Protocol Set (PPS)</td>
<td>483 (89.4)</td>
<td>476 (87.0)</td>
<td>386 (89.6)</td>
<td>1345 (88.6)</td>
</tr>
<tr>
<td>Per-Protocol Set for Incontinence (PPS-I)</td>
<td>373 (69.1)</td>
<td>368 (67.3)</td>
<td>291 (67.5)</td>
<td>1032 (68.0)</td>
</tr>
</tbody>
</table>

Source: Table 17 in study 3003 report.
<sup>a</sup> Total number (N) of subjects in the Randomized Set.

### Study 3004

A total of 506 patients were randomized for study 3004. The study population was enrolled from a total of 109 sites, all located in the U.S. The study discontinuation rate was 15%, ranging from 12.8% to 20.9% across the treatment groups. The most common reasons for discontinuation from the study were withdrawal of consent, lost to follow-up and adverse events.

### Table 4: Summary of Subject Disposition – Study 3004

<table>
<thead>
<tr>
<th></th>
<th>40-weeks Vibegron 75mg (N=92) n (%)</th>
<th>52-weeks Vibegron 75mg (N=182) n (%)</th>
<th>40-weeks Tolterodine ER 4mg (N=91) n (%)</th>
<th>52-weeks Tolterodine ER 4mg (N=141) n (%)</th>
<th>Overall (N=506) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>92 (100)</td>
<td>182 (100)</td>
<td>91 (100)</td>
<td>141 (100)</td>
<td>506 (100)</td>
</tr>
<tr>
<td>Took at Least One Dose of Double-Blind Medication in Study 3004</td>
<td>92 (100)</td>
<td>181 (99.5)</td>
<td>91 (100)</td>
<td>141 (100)</td>
<td>505 (99.8)</td>
</tr>
<tr>
<td>Completed the Study</td>
<td>79 (85.9)</td>
<td>156 (85.7)</td>
<td>72 (79.1)</td>
<td>123 (87.2)</td>
<td>430 (85.0)</td>
</tr>
<tr>
<td>Discontinued from the Study</td>
<td>13 (14.1)</td>
<td>26 (14.3)</td>
<td>19 (20.9)</td>
<td>18 (12.8)</td>
<td>76 (15.0)</td>
</tr>
<tr>
<td>Withdrew Consent</td>
<td>6 (6.5)</td>
<td>11 (6.0)</td>
<td>7 (7.7)</td>
<td>8 (5.7)</td>
<td>32 (6.3)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>4 (4.3)</td>
<td>6 (3.3)</td>
<td>3 (3.3)</td>
<td>2 (1.4)</td>
<td>15 (3.0)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>1 (1.1)</td>
<td>3 (1.6)</td>
<td>4 (4.4)</td>
<td>4 (2.8)</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.1)</td>
<td>3 (1.6)</td>
<td>4 (4.4)</td>
<td>1 (0.7)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Subject withdrawn due to PI</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
<td>1 (0.7)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1 (0.7)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Subject withdrawn due to sponsor</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Protocol Deviation</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Table 13 in Study 3004 report.

The efficacy analysis sets for study 3004 are as follows:
• Full Analysis Set Extension (FAS-Ext): all randomized OAB patients who took at least one dose of double-blind study treatment in study 3004 and had at least one subsequent evaluable change from baseline micturition measurement in this study.
• Full Analysis Set Extension for Incontinence (FAS-Ext-I): all randomized OAB Wet patients who were included in the FAS-I population in study 3003, who took at least one dose of double-blind study treatment in study 3004 and had at least one subsequent evaluable change from baseline (3004) urge urinary incontinence measurement.
• Per-Protocol Set Extension (PPS-Ext): FAS-Ext excluding patients with important deviations from the protocol that may substantially affect the results of the efficacy endpoints.
• Per-Protocol Set Extension for incontinence (PPS-Ext-I): and FAS-Ext-I excluding patients with important deviations from the protocol that may substantially affect the results of the efficacy endpoints.

<table>
<thead>
<tr>
<th>Table 5 Summary of Efficacy Analysis Sets - Study 3004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>40-weeks Vibegron 75mg (N=92)</td>
</tr>
<tr>
<td>52-weeks Vibegron 75mg (N=182)</td>
</tr>
<tr>
<td>40-weeks Tolterodine ER 4mg (N=91)</td>
</tr>
<tr>
<td>52-weeks Tolterodine ER 4mg (N=141)</td>
</tr>
<tr>
<td>Overall (N=506)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>90 (97.8)</td>
</tr>
<tr>
<td>176 (96.7)</td>
</tr>
<tr>
<td>83 (91.2)</td>
</tr>
<tr>
<td>136 (96.5)</td>
</tr>
<tr>
<td>485 (95.8)</td>
</tr>
<tr>
<td>69 (75.0)</td>
</tr>
<tr>
<td>143 (78.6)</td>
</tr>
<tr>
<td>64 (70.3)</td>
</tr>
<tr>
<td>106 (75.2)</td>
</tr>
<tr>
<td>382 (75.5)</td>
</tr>
<tr>
<td>83 (90.2)</td>
</tr>
<tr>
<td>162 (89.0)</td>
</tr>
<tr>
<td>75 (82.4)</td>
</tr>
<tr>
<td>126 (89.4)</td>
</tr>
<tr>
<td>446 (88.1)</td>
</tr>
<tr>
<td>64 (69.6)</td>
</tr>
<tr>
<td>130 (71.4)</td>
</tr>
<tr>
<td>58 (63.7)</td>
</tr>
<tr>
<td>97 (68.8)</td>
</tr>
<tr>
<td>349 (69.0)</td>
</tr>
</tbody>
</table>

Source: Table 15, Study 3004 report.

3.2.3.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of the treatment groups are summarized in the Appendix (Table 17 and Table 18) for each of the two studies. Approximately 90% of patients in Study 3003 were from U.S. and 10% from non-U.S. regions. All patients in study 3004 were from U.S. In both studies, the majority of patients were White (78.3% for study 3003; 76.6% for study 3004). The percentages of female patients were 85.2% for study 3003, and 78.2% for study 3004. The mean age of patients was 60.2 years in both studies. The treatment groups were well balanced with respect to age, sex, race, region, OAB type (wet vs. dry), and prior use in the last 12 months of anticholinergics or beta-3 agonists. OAB-type was the investigator-defined baseline OAB categorization based on protocol inclusion/exclusion criteria and used as randomization strata. Unless otherwise stated, for the purposes of the analyses, OAB type (i.e. as randomized) were used.

3.2.4 Statistical Methodologies

3.2.4.1 Analysis of Co-primary Efficacy Endpoints

Study 3003
In general, the FAS was used for analyzing all non-incontinence efficacy endpoints. The FAS-I was used for all incontinence efficacy endpoints; these were the endpoints related to urge urinary incontinence.
(UUI) episodes and total incontinence episodes.

- **Change from baseline in average number of daily micturitions at Week 12**

The change from baseline in average number of daily micturitions at Week 12 was analyzed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation. The analysis model included terms for treatment, visit, OAB type (wet vs. dry), sex (female vs. male), region (US vs. non-US), baseline score, and interaction of visit by treatment and an unstructured covariance matrix was used to model the correlation among repeated measurements. No imputation of missing data was required for this analysis.

Estimates of least-squares means, with standard errors, and 95% CIs for each treatment group (placebo, vibegron and tolterodine) and for treatment differences between treatment groups (vs. placebo) were presented. The primary comparison was between vibegron and placebo at Week 12.

- **Change from baseline in urge urinary incontinence (UUI) episodes at Week 12**

The change from baseline UUI episodes was analyzed using a similar MMRM model as for the micturition endpoint described above excluding the term of OAB type since the UUI endpoint was only collected for OAB wet patients. The FAS-I was the analysis population for the UUI endpoint.

**Study 3004**
Efficacy evaluation for study 3004 was the secondary objective.

### 3.2.4.2 Analysis of Secondary Efficacy Endpoints

**Study 3003**
The secondary efficacy endpoints that were pre-specified for hypothesis testing are listed in section 3.2.2.1.

The CFB in urgency episodes at Week 12, CFB in total incontinence at Week 12, and CFB in average volume voided per micturition at Week 12 were analyzed in a similar manner as the co-primary efficacy endpoints. The CFB analysis for the coping score was calculated at Week 12 and analyzed in a similar manner as the primary endpoints, but with only one post-baseline assessment.

Percent of OAB wet patients with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12; percent of OAB wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12; and percent of all OAB patients with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 12, each was analyzed using the Cochran-Mantel-Haenszel risk difference estimate stratified by sex (female vs. male). The CMH estimated risk difference between vibegron and placebo with 95% CI and p-value at Week 12 were provided.

**Study 3004**
No formal comparisons of vibegron vs. tolterodine are planned; all efficacy analyses were considered descriptive.

The FAS-Ext was the analysis population for the micturition endpoint. A mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation was used as the primary analysis.
model for change from baseline in average number of daily micturitions at Week 52. The analysis model included terms for treatment, visit, OAB type (wet vs. dry), sex (female vs. male), baseline score, and interaction of visit by treatment. This model included data from Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, Week 44 and Week 52. Model was restricted to patients who were randomized to a planned 52-weeks of active treatment. No imputation of missing data was required for this analysis.

CFB at Week 52 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients was analyzed using the same model as described above. CFB at Week 52 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet patients and CFB at Week 52 in average number of total urinary incontinence episodes over 24 hours in OAB wet patients were also analyzed in a similar manner excluding OAB type in the model and the analysis population was FAS-EXT-I.

### 3.2.4.3 Sensitivity analysis

**Study 3003**

For Study 3003, the Applicant pre-planned the following sensitivity analysis for each of the co-primary efficacy endpoints,

- Analysis of covariance (ANCOVA) using multiple imputation (MI) for missing data on FAS/FAS-I and PPS/PPS-I
- ANCOVA using LOCF for missing data on FAS/FAS-I and PPS/PPS-I
- Same MMRM analysis as the primary analysis on PPS
- Same MMRM analysis as the primary analysis using OAB-d type (instead of OAB type)
- Same MMRM analysis as the primary analysis excluding duplicate patients

The Applicant also conducted post-hoc analysis that excluded sites 10-156 and 27-105 from the FAS due to the data anomaly issues.

### 3.2.5 Study Results

#### 3.2.5.1 Results for the co-primary efficacy endpoints

**Study 3003**

The Applicant’s analysis results for the co-primary efficacy endpoints are shown in Table 6 and Table 7 for study 3003. Vibegron 75 mg dose demonstrated statistically significant improvements in the co-primary efficacy endpoints compared to the placebo group. At Week 12, compared with placebo group, the Vibegron reduced 0.5 more micturitions and 0.6 more UUI episodes in the change from baseline per 24 hours.
Table 6: Change from Baseline in Average Daily Number of Micturitions at Week 12 (FAS) – Study 3003

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 520</th>
<th>Vibegron 75 mg N = 526</th>
<th>Tolterodine ER 4 mg N = 417</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>520</td>
<td>526</td>
<td>417</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.7 (4.01)</td>
<td>11.3 (3.42)</td>
<td>11.5 (3.15)</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>475</td>
<td>492</td>
<td>378</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.1 (3.34)</td>
<td>9.3 (3.48)</td>
<td>9.6 (3.30)</td>
</tr>
<tr>
<td>LS mean change (SE)</td>
<td>-1.3 (0.14)</td>
<td>-1.8 (0.14)</td>
<td>-1.6 (0.15)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.6 to -1.0</td>
<td>-2.1 to -1.5</td>
<td>-1.9 to -1.3</td>
</tr>
<tr>
<td>LS mean difference vs. placebo (SE)</td>
<td>-0.5 (0.15)</td>
<td>-0.3 (0.16)</td>
<td>-0.6 to 0.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0001</td>
<td>0.0988*</td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 23 in study 3003 report.
Note: Mixed model for repeated measures (MMRM) includes study visit, OAB type, sex, region, baseline number of micturitions and treatment by study visit interaction. Hypothesis testing was only performed for vibegron vs. placebo.
*The P-value for the comparison between tolterodine ER and placebo is nominal, not controlled for multiplicity.

Table 7: Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes at Week 12 (FAS-I) – Study 3003

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 405</th>
<th>Vibegron 75 mg N = 403</th>
<th>Tolterodine ER 4 mg N = 319</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>405</td>
<td>403</td>
<td>319</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.5 (3.05)</td>
<td>3.4 (2.89)</td>
<td>3.4 (2.59)</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>372</td>
<td>383</td>
<td>286</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.0 (2.48)</td>
<td>1.5 (2.45)</td>
<td>1.6 (2.04)</td>
</tr>
<tr>
<td>LS mean change (SE)</td>
<td>-1.4 (0.13)</td>
<td>-2.0 (0.13)</td>
<td>-1.8 (0.14)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.7 to -1.2</td>
<td>-2.3 to -1.8</td>
<td>-2.1 to -1.5</td>
</tr>
<tr>
<td>LS means difference (SE)</td>
<td>-0.6 (0.14)</td>
<td>-0.4 (0.15)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.9 to -0.3</td>
<td>-0.7 to -0.1</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>0.0123*</td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 25 in study 3003 report.
Notes: Mixed model for repeated measures (MMRM) included study visit, sex, region, baseline number of UI/UI episodes and treatment by study visit interaction. Hypothesis testing was only performed for vibegron vs. placebo.
*The P-value for the comparison between tolterodine ER and placebo is nominal, not controlled for multiplicity.

Figure 3 and Figure 4 demonstrate the least square (LS) mean estimates of change from baseline in each co-primary efficacy endpoints over time by study visit. For each of the co-primary endpoints, there was consistent decrease from baseline over the duration of the study to Week 12 for each treatment group. The treatment effect for vibegron vs. placebo maintained through Week 12.
The results of all planned sensitivity analyses within the FAS/FAS-I and the PPS/PPS-I for the co-primary endpoints assessing change from baseline at Week 12 were consistent with the results of the primary endpoint analysis in demonstrating statistical superiority of vibegron over placebo. Additionally, the results of the post-hoc sensitivity analyses that excluded sites 10-156 and 27-105 from the FAS were consistent with the results of the primary endpoint analysis in demonstrating statistical superiority of vibegron over placebo for change from baseline at Week 12.
3.2.5.2 Results for secondary efficacy endpoints

**Study 3003**
The analysis results for the ranked secondary efficacy endpoints are presented in Table 8 to Table 13. At baseline, the average daily number of urgency episodes was about 8 and was similar across the three treatment groups. At Week 12, vibegron 75 mg reduced 0.7 more urgency episodes from baseline in the average daily number of urgency episodes as compared with placebo treatment (p = 0.0020).

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 520</th>
<th>Vibegron 75 mg N = 526</th>
<th>Tolterodine ER 4 mg N = 417</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>520</td>
<td>526</td>
<td>417</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.1 (4.67)</td>
<td>8.1 (4.40)</td>
<td>7.9 (3.88)</td>
</tr>
<tr>
<td><strong>Week 12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>475</td>
<td>492</td>
<td>378</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.8 (4.47)</td>
<td>5.29 (4.50)</td>
<td>5.36 (4.43)</td>
</tr>
<tr>
<td>LS mean change (SE)</td>
<td>-2.0 (0.19)</td>
<td>-2.7 (0.19)</td>
<td>-2.5 (0.21)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-2.4 to -1.7</td>
<td>-3.1 to -2.3</td>
<td>-2.9 to -2.0</td>
</tr>
<tr>
<td>LS mean difference vs. placebo (SE)</td>
<td>-0.7 (0.22)</td>
<td>-0.4 (0.23)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.1 to -0.2</td>
<td>-0.9 to 0.0</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0020</td>
<td>0.0648*</td>
<td></td>
</tr>
</tbody>
</table>

Comparing to placebo group, 16.5% more OAB-wet patients in vibegron 75 mg group achieved ≥ 75% reduction from baseline at Week 12 in average daily number of UI episodes (p < 0.0001). And 6.3% more OAB-wet patients in vibegron 75 mg group achieved 100% reduction from baseline at Week 12 in average daily number of UI episodes (p = 0.0360).

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 405</th>
<th>Vibegron 75 mg N = 403</th>
<th>Tolterodine ER 4 mg N = 417</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with at least 75% reduction in UI from baseline at Week 12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted n (%)</td>
<td>133 (32.8)</td>
<td>199 (49.3)</td>
<td>135 (42.2)</td>
</tr>
<tr>
<td>CMH Difference</td>
<td>16.5</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>9.7 to 23.4</td>
<td>2.1 to 16.7</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td>0.0120*</td>
<td></td>
</tr>
<tr>
<td><strong>Patients with 100% reduction in UI from baseline at Week 12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted n (%)</td>
<td>77 (19.0)</td>
<td>102 (25.3)</td>
<td>67 (20.9)</td>
</tr>
<tr>
<td>CMH Difference</td>
<td>6.3</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.4 to 12.1</td>
<td>-4.1 to 7.8</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0360</td>
<td>0.5447*</td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 28 in study 3003 report.
Notes: MMRM model included study visit, OAB type, sex, region, baseline number of micturitions and treatment by study visit interaction.
*The P-value for the comparison between tolterodine ER and placebo is nominal, not controlled for multiplicity.
Comparing to placebo group, there were 6.8% more patients in vibegron 75 mg group achieved ≥ 50% reduction from baseline at Week 12 in average daily number of urgency episodes (p = 0.0235).

### Table 10: Urgency Episode 50% Responder Analysis at Week 12 (FAS) - Study 3003

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 520</th>
<th>Vibegron 75 mg N = 526</th>
<th>Tolterodine ER 4 mg N = 417</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 50% reduction in urgency episodes from baseline at Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted n (%)</td>
<td>171 (32.8)</td>
<td>208 (39.5)</td>
<td>152 (36.4)</td>
</tr>
<tr>
<td>CMH Difference</td>
<td></td>
<td>6.8</td>
<td>3.7</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.9 to 12.7</td>
<td>-2.5 to 10.0</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.0235</td>
<td>0.2400*</td>
</tr>
</tbody>
</table>

Source: Table 34 in study 3003 report
Notes: MI was used to impute values missing for any reason at the weeks analyzed.
The difference in proportion, corresponding CI and p-value were calculated using the CMH method stratified by sex.
*The P-value for the comparison between tolterodine ER and placebo is nominal, not controlled for multiplicity.

At baseline, the average daily number of incontinence episodes was about 4 in the OAB-wet patients and was similar across the 3 treatment groups. At Week 12, vibegron 75 mg reduced 0.7 more incontinence episodes from baseline as compared with placebo treatment (p < 0.0001).

### Table 11: Change from Baseline in Total Incontinence at Week 12 (FAS-I) – Study 3003

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 405</th>
<th>Vibegron 75 mg N = 403</th>
<th>Tolterodine ER 4 mg N = 319</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>405</td>
<td>403</td>
<td>319</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.2 (3.82)</td>
<td>4.1 (3.63)</td>
<td>4.1 (3.07)</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>372</td>
<td>383</td>
<td>286</td>
</tr>
<tr>
<td>LS mean change (SE)</td>
<td>-1.6 (0.15)</td>
<td>-2.3 (0.15)</td>
<td>-2.0 (0.16)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.9 to -1.3</td>
<td>-2.6 to -2.0</td>
<td>-2.4 to -1.7</td>
</tr>
<tr>
<td>LS means difference (SE)</td>
<td>-0.7 (0.16)</td>
<td>-0.5 (0.17)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.0 to -0.4</td>
<td>-0.8 to -0.1</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>0.0074*</td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 36 in study 3003 report.
Notes: MMRM model included study visit, sex, region, baseline number of incontinence episodes, and treatment by study visit interaction.
*The P-value for the comparison between tolterodine ER and placebo is nominal, not controlled for multiplicity.

For more detail review on the validity and clinical meaningful change of OAB-q LF coping score, please refer to COA reviewer's consultation review.
At baseline, the average volume voided per micturition was about 147 to 155 mL and was similar across the 3 treatment groups. At Week 12, the average volume voided per micturition increased 21.2 mL more in the vibegron 75 mg treated group from baseline as compared with placebo group (p < 0.0001).

**Table 13: Change from Baseline in Average Volume Voided per Micturition (mL) at Week 12 (FAS) – Study 3003**

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 520</th>
<th>Vibegron 75 mg N = 526</th>
<th>Tolterodine ER 4 mg N = 417</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>514</td>
<td>524</td>
<td>415</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>148.3 (60.67)</td>
<td>155.4 (63.07)</td>
<td>147.0 (60.79)</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>478</td>
<td>490</td>
<td>375</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>149.1 (69.42)</td>
<td>175.3 (81.78)</td>
<td>162.1 (72.96)</td>
</tr>
<tr>
<td>LS mean change (SE)</td>
<td>2.2 (3.28)</td>
<td>23.5 (3.26)</td>
<td>15.5 (3.52)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-4.2 to 8.7</td>
<td>17.1 to 29.9</td>
<td>8.6 to 22.4</td>
</tr>
<tr>
<td>LS means difference (SE)</td>
<td>21.2 (3.52)</td>
<td>13.3 (3.76)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>14.3 to 28.1</td>
<td>5.9 to 20.7</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 39 in study 3003 report.
Notes: MMRM model included study visit, OAB type, sex, region, baseline volume (mL) and treatment by study visit interaction.
*The P-value for the comparison between tolterodine ER and placebo is nominal, not controlled for multiplicity.

**Study 3004**

Table 14 presents the results for the secondary efficacy endpoints at Week 52 in study 3004. Figure 5 to Figure 8 presents the secondary efficacy endpoints through the 52 weeks. For patients treated with vibegron throughout 52 weeks, the reduction from baseline observed at Week 12 maintained over 52 weeks.
Table 14: Secondary Endpoint Analysis: Change from Baseline at Week 52 - Study 3004

<table>
<thead>
<tr>
<th>Change from Baseline at Week 52</th>
<th>52-weeks Vibegron 75mg</th>
<th>52-weeks Tolterodine ER 4mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Daily Micturitions (All Subjects)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n=152</td>
<td>n=120</td>
</tr>
<tr>
<td>Least Squares (LS) Means (Standard Error [SE])</td>
<td>-2.4 (0.24)</td>
<td>-2.0 (0.26)</td>
</tr>
<tr>
<td>95% Confidence Interval (CI)</td>
<td>-2.9 to -2.0</td>
<td>-2.5 to -1.5</td>
</tr>
<tr>
<td><strong>Average Daily Urge Urinary Incontinence (OAB Wet Subjects)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n=125</td>
<td>n=91</td>
</tr>
<tr>
<td>LS Means (SE)</td>
<td>-2.2 (0.15)</td>
<td>-1.7 (0.17)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-2.5 to -1.9</td>
<td>-2.0 to -1.3</td>
</tr>
<tr>
<td><strong>Average Daily Urgency Episodes (All Subjects)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n=152</td>
<td>n=120</td>
</tr>
<tr>
<td>LS Means (SE)</td>
<td>-3.4 (0.34)</td>
<td>-3.2 (0.37)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-4.0 to -2.7</td>
<td>-4.0 to -2.5</td>
</tr>
<tr>
<td><strong>Average Daily Total Urinary Incontinence Episodes (OAB Wet Subjects)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n=125</td>
<td>n=91</td>
</tr>
<tr>
<td>LS Means (SE)</td>
<td>-2.5 (0.17)</td>
<td>-1.9 (0.19)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-2.8 to -2.2</td>
<td>-2.3 to -1.6</td>
</tr>
</tbody>
</table>

Source: Table 1 in study 3004 report.

<sup>a</sup> FAS-Ext population; vibegron N=176, tolterodine N=136

<sup>b</sup> FAS-Ext-I population; vibegron N=143, tolterodine N=106

Figure 5: Secondary Endpoint Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Micturitions (FAS-Ext) – Study 3004

Source: Figure 3 in study 3004 report.
Figure 6: Secondary Endpoint Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes (FAS-Ext-I) -Study 3004

Source: Figure 4 in study 3004 report.

Figure 7: Secondary Endpoint Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Urgency Episodes (FAS-Ext) -Study 3004

Source: Figure 5 in study 3004 report.
3.3 Evaluation of Safety

Refer to the clinical reviewer’s report for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Efficacy of vibegron 75 mg on the co-primary endpoints was also evaluated by subgroups defined by region, age, race, sex, OAB type and OAB-d type. The categories for each subgroup variable are defined in the following table.

<table>
<thead>
<tr>
<th>Grouping variable</th>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>US, non-US</td>
</tr>
<tr>
<td>Age group</td>
<td>&lt; 65 years, &gt;= 65 years</td>
</tr>
<tr>
<td>Race</td>
<td>White, Other</td>
</tr>
<tr>
<td>Sex</td>
<td>Male, Female</td>
</tr>
<tr>
<td>OAB type</td>
<td>Wet or Dry</td>
</tr>
<tr>
<td>OAB-d type</td>
<td>Wet or Dry</td>
</tr>
</tbody>
</table>

The OAB-type is the investigator-defined baseline OAB categorization based on protocol inclusion/exclusion criteria and used as randomization strata.

OAB-d Type is categorized based on baseline diary data, as follows:

- Wet: Patients are considered Wet according to the following criteria:
  - An average of ≥ 8.0 micturitions per Diary Day; and,
  - An average of ≥ 1.0 UUI episodes per Diary Day; and,
o If stress urinary incontinence (SUI) is present, the total number of UUI episodes must be greater than the total number of SUI episodes.

• Dry: Patients are considered Dry according to the following criteria:
  o An average of ≥ 8.0 micturitions per Diary Day; and,
  o An average of ≥ 3.0 urgency episodes per Diary Day; and,
  o An average of < 1.0 UUI episodes per Diary Day

For each coprimary endpoint, the subgroup by treatment group interaction was analyzed using a MMRM model which include treatment group, visit, treatment by visit interaction, OAB type (wet vs. dry, this variable was not used for analysis of UUI), sex, baseline score, subgroup variable, and the interaction of the subgroup variable by treatment.

The LS mean estimates for mean changes from baseline, SE’s, two-sided 95% CIs within each treatment group as well as the difference in adjusted mean change from baseline and corresponding two-sided 95% CIs between each treatment group and the placebo group for each subgroup level were calculated. In addition, the corresponding p-value for subgroup by treatment interaction term was calculated from the model.

The subgroup analyses results are presented using a forest plot (see Figure 9 and Figure 10) for each coprimary efficacy endpoint.

**Figure 9: Forest Plot of Vibegron Treatment Effect vs Placebo on Average Daily Number of Urgency Episodes at Week 12 by Subgroup - Full Analysis Set (FAS)**

<table>
<thead>
<tr>
<th>Subgroups (n[V], n[P])</th>
<th>Vibegron (N=526)</th>
<th>Placebo (N=520)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US (472, 463)</td>
<td>-1.9</td>
<td>-1.4</td>
<td>-0.5</td>
</tr>
<tr>
<td>Non-US (54, 57)</td>
<td>-1.8</td>
<td>-1.4</td>
<td>-0.4</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (284, 300)</td>
<td>-1.7</td>
<td>-1.5</td>
<td>-0.2</td>
</tr>
<tr>
<td>≥65 (242, 220)</td>
<td>-1.9</td>
<td>-1.0</td>
<td>-0.9</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (422, 406)</td>
<td>-1.8</td>
<td>-1.3</td>
<td>-0.5</td>
</tr>
<tr>
<td>Other (104, 114)</td>
<td>-1.7</td>
<td>-1.2</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (77, 75)</td>
<td>-1.7</td>
<td>-1.1</td>
<td>-0.6</td>
</tr>
<tr>
<td>Female (449, 445)</td>
<td>-1.9</td>
<td>-1.4</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>OAB Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet (403, 405)</td>
<td>-2.0</td>
<td>-1.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>Dry (123, 115)</td>
<td>-1.6</td>
<td>-0.9</td>
<td>-0.7</td>
</tr>
<tr>
<td><strong>OAB-d Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet (385, 399)</td>
<td>-2.1</td>
<td>-1.6</td>
<td>-0.5</td>
</tr>
<tr>
<td>Dry (126, 108)</td>
<td>-1.7</td>
<td>-0.8</td>
<td>-0.9</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>-1.8</td>
<td>-1.3</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Source: Table 14.2.1.1.10 in study 3003 report; Reviewer’s analysis
4.1 Geographic Region, Age, Race and Sex

Subgroup analyses demonstrated greater reduction in general for the average daily number of micturitions from baseline at Week 12 following treatment with vibegron compared with placebo, when assessing by region (US or non-US), age category (< 65 years or ≥ 65 years), race (white or other), sex (male or female), OAB type (wet or dry), and OAB-d type (wet or dry).

Subgroup analyses generally demonstrated greater reduction from baseline at Week 12 in average daily number of UUI episodes for OAB Wet patients following treatment with vibegron compared with placebo, including when assessing by region (US or non-US), age category (< 65 years or ≥ 65 years), race (white or other), or sex (male or female). Two exceptions to this trend are the LS means difference (vibegron – placebo) was 0.0 at Week 12 for non-white (other) patients and was 0.1 at Week 8 for male patients (i.e., vibegron and placebo were similar).

Reviewer’s analysis

When exploring the data by race and sex subgroups, the reviewer noted that in the “other” race subgroup and in the male patients, the UUI episodes at baseline were imbalanced between the treatment groups. Comparing to placebo group, the vibegron 75 mg group had less UUI episodes at baseline in the “other” race subgroup and male subgroup respectively. This imbalance might contribute to the findings in the two exceptions (see Table 16).

Given the descriptive nature of these analyses and the smaller size of these subgroups, these findings should be interpreted with caution, and no definite conclusions can be drawn.
### Table 16: Average Daily Number of Urge Urinary Incontinence Episodes at Baseline by race and sex (FAS-I) Study 3003

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo N = 405</th>
<th>Vibegron 75 mg N = 403</th>
<th>Tolterodine ER 4 mg N = 319</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race (n, mean[SD])</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>80, 4.01[4.14]</td>
<td>81, 2.82 [2.48]</td>
<td>65, 3.28[2.54]</td>
</tr>
<tr>
<td><strong>Sex (n, mean[SD])</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>364, 3.50[3.05]</td>
<td>361, 3.50[2.92]</td>
<td>284, 3.41[2.62]</td>
</tr>
</tbody>
</table>

Reviewer’s analysis

#### 4.2 Other Special/Subgroup Populations

Subgroup analyses by OAB-type/OAB-d type demonstrated greater reduction for the average daily number of micturitions from baseline at Week 12 following treatment with vibegron compared with placebo, when assessing.

#### 5 SUMMARY AND CONCLUSIONS

##### 5.1 Statistical Issues and Collective Evidence

Study 3003 was designed to evaluate the efficacy of vibegron 75 mg during treatment period of 12 weeks with respect to two co-primary endpoints and selected secondary efficacy endpoints. Study 3004 was an extension study of 3003 with additional 40 weeks of treatment to evaluate the safety and efficacy of long-term use.

##### 5.2 Conclusions and Recommendations

The purpose of this review is to evaluate the efficacy data in support of vibegron in the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. Based on reviewer’s analyses, the results supported the efficacy of vibegron 75 mg in the improvement of the protocol specified co-primary endpoints and the selected secondary efficacy endpoints.

From a statistical perspective, vibegron 75mg was effective in treating OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.
APPENDICES

Demographics and Baseline Characteristics

Table 17 Summary of Patient Demographics and Baseline Characteristics - Study 3003, FAS

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 520</th>
<th>Vibegron 75 mg N = 526</th>
<th>Tolterodine ER 4 mg N = 417</th>
<th>Overall N = 1463</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>59.9 (13.33)</td>
<td>60.8 (13.30)</td>
<td>59.8 (13.19)</td>
<td>60.2 (13.28)</td>
</tr>
<tr>
<td>Age category (years), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>45 (8.7)</td>
<td>40 (7.6)</td>
<td>36 (8.6)</td>
<td>121 (8.3)</td>
</tr>
<tr>
<td>≥ 40 to &lt; 55</td>
<td>111 (21.3)</td>
<td>112 (21.3)</td>
<td>95 (22.8)</td>
<td>318 (21.7)</td>
</tr>
<tr>
<td>≥ 55 to &lt; 65</td>
<td>144 (27.7)</td>
<td>132 (25.1)</td>
<td>120 (28.8)</td>
<td>396 (27.1)</td>
</tr>
<tr>
<td>≥ 65 to &lt; 75</td>
<td>163 (31.3)</td>
<td>167 (31.7)</td>
<td>119 (28.5)</td>
<td>449 (30.7)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>57 (11.0)</td>
<td>75 (14.3)</td>
<td>47 (11.3)</td>
<td>179 (12.2)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (14.4)</td>
<td>77 (14.6)</td>
<td>65 (15.6)</td>
<td>217 (14.8)</td>
</tr>
<tr>
<td>Female</td>
<td>445 (85.6)</td>
<td>449 (85.4)</td>
<td>352 (84.4)</td>
<td>1246 (85.2)</td>
</tr>
<tr>
<td>Benign prostate hyperplasia, yes (male only), n (%)</td>
<td>16 (21.3)</td>
<td>29 (37.7)</td>
<td>22 (33.8)</td>
<td>67 (30.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
<td>0</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>29 (5.6)</td>
<td>27 (5.1)</td>
<td>26 (6.2)</td>
<td>82 (5.6)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>79 (15.2)</td>
<td>74 (14.1)</td>
<td>69 (16.5)</td>
<td>222 (15.2)</td>
</tr>
<tr>
<td>White</td>
<td>406 (78.1)</td>
<td>422 (80.2)</td>
<td>317 (76.0)</td>
<td>1145 (78.3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
<td>5 (1.2)</td>
<td>10 (0.7)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>463 (89.0)</td>
<td>472 (89.7)</td>
<td>376 (90.2)</td>
<td>1311 (89.6)</td>
</tr>
<tr>
<td>Non-US</td>
<td>57 (11.0)</td>
<td>54 (10.3)</td>
<td>41 (9.8)</td>
<td>152 (10.4)</td>
</tr>
<tr>
<td>OAB type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet</td>
<td>405 (77.9)</td>
<td>403 (76.6)</td>
<td>319 (76.5)</td>
<td>1127 (77.0)</td>
</tr>
<tr>
<td>Dry</td>
<td>115 (22.1)</td>
<td>123 (23.4)</td>
<td>98 (23.5)</td>
<td>336 (23.0)</td>
</tr>
<tr>
<td>Prior anticholinergic use in the last 12 months, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85 (16.3)</td>
<td>77 (14.6)</td>
<td>51 (12.2)</td>
<td>213 (14.6)</td>
</tr>
<tr>
<td>Prior beta-3 agonist use in the last 12 months, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27 (5.2)</td>
<td>21 (4.0)</td>
<td>32 (7.7)</td>
<td>80 (5.5)</td>
</tr>
</tbody>
</table>

Source: Table 18, Study 3003 report
<table>
<thead>
<tr>
<th>Variable</th>
<th>40-weeks Vibegron 75mg (N=92) n (%)</th>
<th>52-weeks Vibegron 75mg (N=181) n (%)</th>
<th>40-weeks Tolterodine ER 4mg (N=91) n (%)</th>
<th>52-weeks Tolterodine ER 4mg (N=141) n (%)</th>
<th>Overall (N=505) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry (years), mean (SD)</td>
<td>58.8 (13.69)</td>
<td>62.1 (12.39)</td>
<td>62.1 (12.14)</td>
<td>60.6 (12.98)</td>
<td>61.1 (12.78)</td>
</tr>
<tr>
<td>Age category (years), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>9 (9.8)</td>
<td>11 (6.1)</td>
<td>5 (5.5)</td>
<td>11 (7.8)</td>
<td>36 (7.1)</td>
</tr>
<tr>
<td>≥ 40 to &lt; 55</td>
<td>22 (23.9)</td>
<td>34 (18.8)</td>
<td>16 (17.6)</td>
<td>27 (19.1)</td>
<td>99 (19.6)</td>
</tr>
<tr>
<td>≥ 55 to &lt; 65</td>
<td>25 (27.2)</td>
<td>43 (23.8)</td>
<td>27 (29.7)</td>
<td>40 (28.4)</td>
<td>135 (26.7)</td>
</tr>
<tr>
<td>≥ 65 to &lt; 75</td>
<td>28 (30.4)</td>
<td>70 (38.7)</td>
<td>30 (33.0)</td>
<td>47 (33.3)</td>
<td>175 (34.7)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>8 (8.7)</td>
<td>23 (12.7)</td>
<td>13 (14.3)</td>
<td>16 (11.3)</td>
<td>60 (11.9)</td>
</tr>
<tr>
<td>Sex, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (20.7)</td>
<td>41 (22.7)</td>
<td>21 (23.1)</td>
<td>29 (20.6)</td>
<td>110 (21.8)</td>
</tr>
<tr>
<td>Female</td>
<td>73 (79.3)</td>
<td>140 (77.3)</td>
<td>70 (76.9)</td>
<td>112 (79.4)</td>
<td>395 (78.2)</td>
</tr>
</tbody>
</table>
| Benign prostate hyperplasia (male only), n (%)
  yes | 4 (21.1) | 16 (39.0) | 6 (26.8) | 8 (27.6) | 34 (30.9) |
| Baseline hypertension
  yes | 9 (9.8) | 11 (6.1) | 8 (8.8) | 15 (10.6) | 43 (8.5) |
| Pre-existing hypertension
  yes | 39 (42.4) | 97 (53.6) | 31 (34.1) | 72 (51.1) | 239 (47.3) |
| OAB type
  yes | | | | | |
| Wet | 71 (77.2) | 146 (80.7) | 70 (76.9) | 108 (76.6) | 395 (78.2) |
| Dry | 21 (22.8) | 35 (19.3) | 21 (23.1) | 33 (23.4) | 110 (21.8) |
| Prior anticholinergic use
  yes | 11 (12.0) | 27 (14.9) | 16 (17.6) | 15 (10.6) | 69 (13.7) |
| Prior beta-3 agonist use
  yes | 7 (7.6) | 9 (5.0) | 9 (9.9) | 10 (7.1) | 35 (6.9) |
| Race, n (%) | | | | | |
| American Indian or Alaska Native | 2 (2.2) | 0 | 0 | 0 | 2 (0.4) |
| Asian | 4 (4.3) | 16 (8.8) | 8 (8.8) | 11 (7.8) | 39 (7.7) |
| Black or African American | 14 (15.2) | 23 (12.7) | 10 (11.0) | 26 (18.4) | 73 (14.5) |
| White | 72 (78.3) | 141 (77.9) | 72 (79.1) | 102 (72.3) | 387 (76.6) |
| Other | 0 | 1 (0.6) | 1 (1.1) | 2 (1.4) | 4 (0.8) |

Source: Table 16 in study 3004 report.
Note: Baseline refers to the baseline visit (Visit 3) in Study 3003.
a For benign prostate hyperplasia, percentages are based on the number of males.
b Baseline hypertension is based on baseline vitals.
c Pre-existing hypertension is based on baseline vitals and prior medical history.
d OAB type is as randomized.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JIA GUO
10/28/2020 12:07:37 PM

TSAE YUN D LIN
10/28/2020 02:31:14 PM