CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213006Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	213006
Priority or Standard	Standard
Submit Date(s)	December 25, 2019
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PDUFA Goal Date	December 26, 2020
Division/Office	Division of Urology, Obstetrics, and Gynecology Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine Center for Drug Evaluation and Research
Reviewer Name(s)	Debuene Chang MD
Review Completion Date	December 9, 2020
Established/Proper Name	vibegron
(Proposed) Trade Name	(Proposed) Gemtesa®
Applicant	Urovant
Dosage Form(s)	75 mg oral
Applicant Proposed Dosing Regimen(s)	75 mg oral tablet once daily
Applicant Proposed Indication(s)/Population(s)	Treatment for overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

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Glossary

ABPM	ambulatory blood pressure monitoring
AC	advisory committee
ADR	adverse drug reactions
AE	adverse event
AECI	AEs of clinical interest
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BPH	benign prostatic hyperplasia/hypertrophy
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDF/eCDF	cumulative distribution function/ empirical cumulative distribution function
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFB	change from baseline
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CMC	chemistry, manufacturing, and controls
COA	clinical outcomes assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DCN	Division of Cardiovascular and Renal Products
DCOA	Division of Clinical Outcomes Assessment
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EMA	European Medicines Agency
ER	extended release
ETASU	elements to assure safe use
FAS	full analysis set
FAS-ext	full analysis set-extension population

FAS-ext-I	full analysis set-extension population-incontinence
FAS-I	full analysis set-incontinence
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HRQL	Health Related Quality of Life scale
IBS	irritable bowel syndrome
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IRT	FDA interdisciplinary review team
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MACCE	major adverse cardiovascular and cerebrovascular event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	mixed model for repeat measures
MRHD	maximal recommended human dose
NAI	no action indicated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NDO	neurogenic detrusor overactivity
NME	new molecular entity
NOAEL	no adverse effect level
NOEL	no effect level
OAB	overactive bladder
OAB-q LF	OAB questionnaire – Long form
OAB-dry	overactive bladder-dry
OAB-wet	overactive bladder-wet
OCS	Office of Computational Science
OD	once daily
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGI	Patient Global Impression Questionnaire
PGI-Control	Patient Global Impression of Control Questionnaire
PGI-frequency	Patient Global Impression Questionnaire of urinary frequency

PGI-Severity	Patient Global Impression of Severity Questionnaire
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PVD	patient voiding diary
PVR	post void (urinary) residual
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGE	special government employee
SOC	standard of care
SUI	stress urinary incontinence
TEAE	treatment emergent adverse event
UTI	urinary tract infection
UUI	urge urinary incontinence
β3-AR	beta-3 adrenergic receptor

1. Executive Summary

1.1. Product Introduction

Vibegron (RVT-901, URO-901, MK-4618, KRP-114V), a new molecular entity (NME), is a selective agonist of the human beta-3 adrenergic receptor (β3-AR), developed for treatment of overactive bladder (OAB) with 75 mg oral daily dosage.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Sponsor has provided substantial evidence of effectiveness to support approval of this application. See section 7.3 for details.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

1. Introduction: Vibegron, a new molecular entity, is a selective agonist of the human beta-3 adrenergic receptor (β3-AR), developed for treatment of overactive bladder (OAB) with 75 mg oral daily dosage.
   Recommendation: Approval
2. Analysis of Condition and Current Treatment Options: OAB is highly prevalent in the US, increases with age, affecting approximately 33% of people ≥ age 75. OAB is a chronic condition which has adverse impact on quality of life, especially in OAB with incontinence. Current treatments are modestly effective and include first-line behavior therapy with weight loss and pelvic floor therapy. Second-line pharmacologic agents have modest or low efficacy with side effects. There is a need for more efficacious pharmacologic therapy with reduced side effects, especially for continence control.
3. Benefit: The clinical studies demonstrated statistically significant but very modest benefits for urinary frequency, urge urinary incontinence and "urgency" (need to urinate immediately) reductions when compared to placebo. Responder analyses for these endpoints showed that while some patients will have clinical meaningful efficacy, the majority will not. This product will not fulfil the need for more efficacious therapy for OAB, based on the study results.
4. Risk: Safety issues identified in the postmarketing reports from Japan for urinary retention, rash/ allergic skin disorders and constipation can be mitigated with labeling.
5. Analysis and Recommendation: Overall benefit-risk assessment indicate that vibegron will have minimal to modest efficacy in some patients but the majority of patients may not achieve clinical meaningful reductions in frequency, urge urinary incontinence, and "urgency" (need to urinate immediately). The risks identified from the safety data do not identify an increase in BP for vibegron unlike other products in this class and the identifiable risks of urinary retention, skin rash/ allergic disorders, and constipation can be managed with labeling. Based on this assessment, vibegron can be an addition to second-line therapy to the β3 adrenergic agonist armamentarium but will likely have no efficacy benefits over currently available therapies. However, vibegron may have a safety advantage as the safety data does not show a blood pressure signal. Based on this benefit-risk assessment, the recommendation is for approval.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Overactive Bladder includes: 1) urinary urgency 2) urinary frequency 3) nocturia and 4) urgency incontinence • OAB highly prevalent in ~ 1 in 7 adults across both sexes in US • Increases with age, affecting ~ 33% age ≥ 75 years • Adverse impact on health-related quality of life especially for patients with urinary incontinence, chronic, and not life-threatening	Although not a life-threatening disorder, OAB can impact quality of life with increase social isolation and depression. Patients seek symptomatic relief, especially for urinary incontinence. Greater impact on older adults as more prevalent in these populations.
Current Treatment Options	• First-line therapy is behavioral therapy including weight loss, pelvic floor therapy, and fluid management. • Second-line therapy include 1) antimuscarinic agents 2) β3-adrenoceptor agonist agent • Third-line options include 1) botulinum toxin intravesical injections 2) peripheral nerve stimulation 3) neuromodulation with surgical implantation of electrical stimulator	AUA Guidance (2019) identify behavioral therapy with weight loss as first-line therapy which is as effective for OAB treatment as second-line pharmacologic agents. But, first-line therapy takes time and effort by both patients and medical providers in the US medical system. Second-line therapy are the available pharmacologic agents of antimuscarinic or β3-adrenoceptor agonist agent which are commonly prescribed to patients. All currently approved pharmacologic agents have modest efficacy when compared to placebo and all have side-effects. Specifically,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		➢ Antimuscarinic agents AEs include dry mouth, constipation, blurred vision, contraindicated for glaucoma, urinary retention, dyspepsia, and impaired cognitive function ➢ β3-adrenoceptor agonist (mirabegron) Common AEs include hypertension, nasopharyngitis, UTI and headache As a chronic pharmacologic agent for symptomatic relief of OAB, patients will discontinue therapy for lack of efficacy or side effects. There is an unmet need for more efficacious OAB agents which can control incontinence with minimal side effects as the current available agents are minimally efficacious compared to placebo. Third-line therapy are recommended in patients who are not treated or cannot tolerate first-or second-line therapy for OAB. Neuromodulation requires surgical procedures and not as commonly prescribed for patients.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Benefit</td><td>

Study 3003 studied 1518 patients who were randomized to vibegron 75 mg daily dose, placebo and active-control tolterodine.
High placebo response rate was present across all primary and secondary efficacy endpoint results, consistent with other OAB studies in this patient population.
“Urgency” has been a difficult term to precisely define or characterize clinically resulting in most OAB studies relying on other objective measures. The Sponsor used the term “need to urinate immediately” and not “urgency” in the patient voiding diary (PVD) to define both the urge urinary incontinence (UUI) and urgency episode endpoints from the patient’s perspective. The use of the term “need to urinate immediately” for “urgency” is novel and has not been used to support other OAB products.
The following table summarizes the co-primary endpoints of average daily micturitions, average daily UUI episodes, and key secondary endpoint of urgency which all met statistical significance but the difference from placebo in each endpoint was small between -0.5 to -0.7 episodes per day.

<table>
<tr><th>Parameter</th><th>Placebo</th><th>Vibegron 75 mg</th></tr>
<tr><td colspan="3">Average Daily Number of Micturitions-Co-Primary Endpoint</td></tr>
<tr><td>Baseline mean (n)</td><td>11.75 (520)</td><td>11.31 (526)</td></tr>
<tr><td>Change from Baseline▪ (n)</td><td>-1.3 (475)</td><td>-1.8 (492)</td></tr>
<tr><td>Difference from Placebo</td><td colspan="2">-0.5</td></tr>
<tr><td>95% Confidence Interval</td><td colspan="2">-0.8 to -0.2</td></tr>
<tr><td>p-value</td><td colspan="2"><0.001</td></tr>
<tr><td colspan="3">Average Daily Number of UUI Episodes-Co-Primary Endpoint</td></tr>
<tr><td>Baseline mean (n)</td><td>3.49 (405)</td><td>3.43 (403)</td></tr>
</table>
</td><td>Submitted evidence meets evidentiary standard with the Study 3003 results meeting statistical significance for co-primary endpoints. However, the clinical meaningful analyses of the two co-primary endpoints and key secondary endpoint indicate that the benefits of vibegron 75 mg is small or minimal compared to placebo.

This product will fit into the armamentarium mostly as a second β3-adrenergic agonist following mirabegron with similar low to modest effectiveness. Unlike mirabegron, there is no evidence that this product increases blood pressure, so it may be an alternative therapy for patients.

The Sponsor’s co-primary UUI endpoint and key secondary endpoint, “urgency” used PVD PRO where patients identified “urge to urinate immediately”. Any description of “urgency” in labeling should reflect what patients identified in the PVD PRO of “need to urinate immediately”.</td></tr>
</table>

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><td>Change from Baseline▪ (n)</td><td>-1.4 (372)</td><td>-2.0 (383)</td></tr>
<tr><td>Difference from Placebo</td><td colspan="2">-0.6</td></tr>
<tr><td>95% Confidence Interval</td><td colspan="2">-0.9 to -0.3</td></tr>
<tr><td>p-value</td><td colspan="2"><0.0001</td></tr>
<tr><td colspan="3">Average Daily Number of Urgency Episodes-Key Secondary Endpoint</td></tr>
<tr><td>Baseline mean (n)</td><td>8.13 (520)</td><td>8.11 (526)</td></tr>
<tr><td>Change from Baseline▪ (n)</td><td>-2.0 (475)</td><td>-2.7 (383)</td></tr>
<tr><td>Difference from Placebo</td><td colspan="2">-0.7</td></tr>
<tr><td>95% Confidence Interval</td><td colspan="2">-1.1 to -0.2</td></tr>
<tr><td>p-value</td><td colspan="2">0.0020</td></tr>
<tr><td colspan="3">▪ Least squares mean adjusted for treatment, baseline, sex, geographical region, study visit, and study visit by treatment interaction term</td></tr>
</table>

The three endpoints were analyzed using anchor-based methods to determine clinical meaningful within-patient change threshold with the following conclusions:
➢ Co-Primary Endpoint-Average Daily Number of Micturition: there is minimal separation between the treatment and placebo arms.
➢ Co-Primary Endpoint-Average Daily Number of UUI Episodes: 35.3% vibegron patients had ≥ 90% reduction in the average daily number of UUI episodes compared to 23.7% of placebo patients.
➢ Key Secondary Endpoint-Urgency (Need to Urinate Immediately): 33.7% vibegron patients had ≥60% reduction in the average daily number of urgency episodes compared to 28.1% of placebo patients.
</td><td>Responder analyses for these endpoints showed that while some patients will have clinical meaningful efficacy, the majority will not.</td></tr>
<tr><td>Risk and Risk Management</td><td>• Vibegron has a consistent safety profile across data pools, similar to the findings in Study 3003 and 3004 with balanced findings between vibegron and placebo. There were no clinical meaningful differences found in the pooled studies which appeared to be dose related differences for 50, 75,</td><td>The safety profile is well-characterized and shows relative balance between vibegron and placebo.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	or 100 mg exposures. Subgroup analyses for < 65 years and ≥ 65 years did not show major differences, relative to placebo in the groups but there were higher numbers of AEs seen in the older patient group in vibegron 75 mg compared to placebo with > 2% differences for headaches, dry mouth and upper respiratory tract infections. • Prespecified AEs of clinical interest including select cardiovascular/ vascular AEs, urinary tract/renal AEs, and other predefined AEs were reported with relatively low frequency (~10% subject incidence in 12-week evaluations or ~20% subject incidence in 52-week evaluations) across treatment groups in all pools which was consistent with the findings from Study 3003 and 3004. • BP and vital signs demonstrated no clinically significant BP changes in the ABPM study 1001 as noted in the ABPM IRT consult. Vital signs and cuff pressure measurements in Study 3003 and 3004 are consistent with the findings from the ABPM study. • PVR-There was no clinically relevant change from baseline in postvoid residual volume PVR urine volume at Week 12 for subjects treated with vibegron compared with placebo. • Other safety laboratory analyses, ECGs, and QTc studies do not show clinically meaningful effects of vibegron on safety laboratory parameters (hematology, clinical chemistry, urinalysis, serum β-choriogonadotropin, and urine culture), ECGs, and QTc. • Post marketing experience in Japan, the only worldwide location where the drug has been marketed since September 2018, has identified urinary retention and rash/ allergic skin reaction as well as constipation which are recommended to be included in labeling.	The safety concerns include urinary retention, rash/allergic skin reactions and constipation noted from postmarketing reports in Japan. Risk management of the safety issues can be addressed in labeling with urinary retention added to the Warning section. No REMS or PMRs/PMCs are recommended.

1.4. Patient Experience Data

Patient Voiding Diary (PVD) are PROs used to record co-primary endpoints and some secondary endpoints. Other PROs used in the studies include the OAB-q LF, PGI-Severity, PGI-Frequency in these studies.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1, 6.2, 6.3, 6.4, 6.5 Study endpoints
		☒	Patient reported outcome (PRO)	Sec 6.1, 6.2, 6.3, 6.4, 6.5 Study endpoints
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1.Analysis of Condition

OAB is a clinical syndrome with patients reporting bothersome, urinary symptoms in the absence of neurological conditions. Both the International Urogynecological Association (IUGA) and International Continence Society (ICS) define OAB as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of UTI or other obvious pathology." The 2019 American Urological Association and Society of Female Pelvic Medicine & Urogenital Reconstruction (SUFU) OAB Guidelines (AUA/SUFU 2019), stated that "OAB symptoms consist of four components: urgency, frequency, nocturia and urgency incontinence." These four OAB symptoms include the following:

1) Urgency: Considered the hallmark OAB symptom
    - Defined by the IUGA and ICA as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer."
    - Difficult to precisely define or characterize clinically resulting in most OAB studies relying on other measures for treatment responses
2) Urinary frequency
    - Measured with patient reported voiding diary
    - Multifactorial etiologies and variable depending on hours of sleep, fluid intake, comorbid conditions etc
3) Nocturia
    - Defined as interruption of sleep one or more times because of the need to void
    - Multifactorial etiologies such as excessive nighttime urine production, sleep apnea, etc.
4) Urgency urinary incontinence
    - Defined as the involuntary leakage of urine, associated with a sudden compelling desire to void
    - Measured with voiding diary for number of voids and pads for quantity of voids

Types of OAB, Wet vs Dry:
OAB without incontinence is sometimes referred to as "OAB Dry". As a correlate, "OAB Wet" is OAB with a component of urgency urinary incontinence. One-third of patients with OAB have OAB Wet with accompanying incontinence.

Types of Urinary Incontinence:
OAB with urinary incontinence (OAB Wet) is not the only type of urinary incontinence. Stress urinary incontinence (SUI), defined as urinary incontinence with an involuntary loss of urine on effort or physical exertion (e.g. Sporting activities, coughing, sneezing, etc.) differs from OAB. The following are types of urinary incontinence classifications:

1) OAB with urgency urinary continence-"OAB Wet"
2) SUI
3) Mixed urinary incontinence with components of both "OAB Wet" and SUI to varying degrees with classifications of the predominant type of incontinence:
    - predominant urgency component
    - predominant stress component.

OAB is highly prevalent and affects approximately 1 in 7 adults (both men and women) in United States (US) and European populations. Prevalence increases with age, with OAB affecting approximately one-third of people 75 years and older.

The consequences of OAB are broad and include direct medical effects and an adverse impact to health-related quality of life. The condition can be highly disruptive and distressing and significantly impact normal daily functions and sleep.

2.2. Analysis of Current Treatment Options

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

Behavior modification including weight loss, pelvic floor training, biofeedback, and fluid management, etc. is the first line treatment recommended by American Urological Association OAB guideline (2019) which noted that it was as effective as currently available agents for OAB treatment.

Other than first-line treatment with behavior modification and weight loss, other pharmacological and device treatments are available, but most have been limited by modest efficacy and/or poor tolerability due to mechanism-based side effects, etc.

Anticholinergics:
The most commonly prescribed OAB medications are of the antimuscarinic drug class (eg, tolterodine [Detrol®], solifenacin [Vesicare®], oxybutynin [Ditropan®]). Their long-term use is limited as patients have had tolerability issues due to relatively high rates of dry mouth and constitutional effects (fatigue, constipation/gastrointestinal effects).

Anticholinergics can cross the blood-brain barrier and there have been recent reports of central nervous system effects with the long-term use of antimuscarinics and other anticholinergic agents, including potentially increased risks of cognitive impairment and dementia. Cognitive deficits can be especially detrimental in the elderly.

β3-AR Agonist

A first-generation β3-AR agonist (mirabegron; Myrbetriq®) was approved for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency, both as a single agent (NDA 202611, approved June 28, 2012) and in combination with the muscarinic antagonist solifenacin succinate (approved 2018).

Mirabegron has shown similar efficacy to antimuscarinics, but has had fewer dose-limiting side effects. As a single agent, the most frequently reported adverse reactions for mirabegron were hypertension, nasopharyngitis, urinary tract infection, and headache. In addition, mirabegron is a cytochrome P450 (CYP)2D6 inhibitor and has been associated with modest increases in the corrected QT interval at supratherapeutic doses.

Table 1: Current OAB Treatment Summary

Treatment Modality	Regimen	Advantages	Disadvantages/AEs
First-Line Therapy Options OAB (AUA 2019 Guidance)			
Behavioral Therapy include weight loss + Pelvic Floor Therapy	• Fluid restriction • bladder training • bladder control strategies • fluid management • pelvic floor muscle training including Kegel's maneuvers with or without biofeedback • weight loss	• First line therapy recommended by AUA Guidance 2019; • Can be as effective as anti-muscarinic medications (see list below) • Low cost and no AEs	• Requires time and effort by patients, caregivers, and clinicians • Biofeedback and pelvic floor therapy can require multiple visits to clinicians and training time
Second-Line Therapy Options OAB			

Antimuscarinic Agents	Daily dose of agents either by patch, topical gel application or oral dosing	Modest efficacy	AEs include: • dry mouth • constipation • blurred vision • contraindicated in uncontrolled glaucoma • Urinary retention • Dyspepsia • Possibly impaired cognitive function
β 3-adrenoceptor agonist-mirabegron approved June 28, 2012 NDA 202611	Daily dose 25mg or 50mg	Similar efficacy to anti-muscarinic meds May have lower rates of dry mouth and constipation compared to anti-muscarinic meds	• Increase hypertension • Moderate CYP2D6 inhibitor • Urinary retention
Third-Line Therapy Options OAB:			
Botulinum Toxin Third-line therapy	Single session 100 units intravesical injection 100 botulinum toxin May need repeat at 6+ months	Can be used in lieu of neuromodulation. Treatment effect may persist for 6+ mos.	Risk of distant spread of toxin hours to weeks after injection Increase risk of retention with need for intermittent catheterizations
Peripheral Nerve Stimulation Third-line therapy	Regularly scheduled visits with placement of external electrode to stimulate either the posterior tibial or pudendal nerve by PTNS	Can be considered prior to neuromodulation Less invasive than neuromodulation No systemic AEs	Local needle site AEs: Discomfort, bleeding, and tingling in leg (posterior tibial site) No substantial evidence of efficacy

Neuromodulation Third-line therapy	Surgical implantation (sacral nerves) of an electrical stimulator	Used in refractory patients	Surgical procedure Device and lead failure and decreased efficacy over time in some patients
Reviewer generated Table			

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Vibegron is a new molecular entity (NME), not currently marketed in the US. See section 3.3 for foreign regulatory actions and marketing history for the Japan market.

This the first Sponsor's vibegron submission for any indication (b) (4)

Three sponsors have conducted the studies in the clinical development program for vibegron:

1. Merck Sharp & Dohme Corp (Merck)
2. Kyorin Pharmaceutical Co, Ltd (Kyorin)
3. Urovant Sciences, GmbH (Urovant)

The original Sponsor, Merck, submitted the opening Investigational New Drug (IND), IND 106410 in January 2010 and conducted the initial vibegron clinical efficacy phase 2b Study 008. Subsequently, Kyorin conducted Phase 3 clinical studies, Studies 301 and 302 in Japan. In 2017, Roivant, the parent company of Urovant, entered into a licensing agreement with Merck and transferred US responsibilities for vibegron to Urovant February 28, 2017.

Kyorin maintains development and commercialization rights to vibegron in Japan, and in September 2018, vibegron was approved for the treatment of OAB in Japan (Tradename Beova®) and started marketing vibegron in Japan at doses 50 mg daily oral dose, titratable to 100mg daily oral dosage.

3.2. Summary of Presubmission/Submission Regulatory Activity

Urovant and previously, Merck, have had multiple engagements with FDA for the proposed registration program for vibegron for the treatment of OAB.

The following table summarizes some of the regulatory history since Merck's opening IND submission in 2010 and includes Merck's transfer to Urovant of US vibegron responsibilities on February 28, 2017:

Table 2: Summary of Vibegron FDA Regulatory Interactions and Activities-IND 1064101

Date	Interaction/Activity
January 29, 2010	Original IND submission (Merck)
September 1, 2011	CAC review of rat carcinogenicity study
April 11, 2012	CAC review of mouse carcinogenicity study
December 4, 2012	DBRUP/DCaRP/IRT review of TQT study (Study 012)
January 19, 2013	Type B End-of-Phase 2 Meeting (Merck)
February 28, 2017	**Ownership of IND transferred to Urovant Sciences GmbH**
July 24, 2017	Type B End-of-Phase 2 Meeting (Urovant)
January 18, 2018	Type C Meeting to Discuss PRO, SAP, and TPP
April 13, 2018	Agreed iPSP
December 17, 2018	NDA application number 213006 pre-assigned
December 21, 2018	Proprietary name (Gemtesa) conditionally acceptable
April 11, 2019	Type C CMC meeting (preliminary written comments only)
June 12, 2019	Type B Pre-NDA Meeting
Source: Reviewer generated Table	

At the July 24, 2017 type B, EOP2 meeting, the FDA agreed that the single phase 3 study 3003 and extension study 3004 studying vibegron 75 mg daily could provide sufficient data to support an NDA submission when submitted with supportive data from Merck Study 008 and Kyorin phase 3 study 301 and Kyorin phase 3 extension study 302.

At the June 12, 2019 type B, Pre-NDA meeting, the FDA agreed that the Sponsor could present clinical efficacy by individual studies without pooling the analysis.

3.3. Foreign Regulatory Actions and Marketing History

Kyorin maintains development and commercialization vibegron rights in Japan, conducted phase 3 studies 301 and 302, and obtained approval for vibegron in Japan in September 2018 for OAB treatment. Japan is the only country worldwide to approve vibegron for any indication to date.

For information on post-marketing data from Japan, see **section 8.9** Safety in the Postmarket Setting.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Office of Scientific Investigations (OSI) audits
OSI consulted and audited the following three high-enroller sites who participated in both Study 3003 and Study 3004:

- Site # 10-133 (Hoover) for reasons of high enrollment (40 patients Study 3003; 18 patients Study 3004), high inspection site automated analysis rank (#6) and better treatment efficacy (-2.86)

- Site # 10-123 (Heller) for reasons of high enrollment (50 patients Study 3003; 10 patients), high inspection site automated analysis rank (#2) and better treatment efficacy (-2.63)

- Site # 10-156 (Pinches III) for reasons of high enrollment (69 patients Study 3003; 35 patients Study 3004), high inspection site automated analysis rank (#3) and "data anomaly".

Of note, the Sponsor's records show that all three of these sites, audited by OSI were inspected by the Sponsor prior to NDA submission: Hoover(site 10-133)-November 5-7, 2018; Heller(site 10-123)-August 28-29, 2018; Pinches III(site 10-156) - August 20-22, 2018.

Site #10-156 (Pinches III) had additional reason "data anomaly" - see section 6.1.2 Study Results Data Quality and Integrity.

The OSI completed inspections of the 3 sites from Study 3003 and 2 out of 3 sites from Study 3004 and deemed all sites inspected in compliance and no action indicated (NAI).

However, the 3rd site, Site 10-133 (Hoover), was inspected only for Study 3003 as the OSI inspector erred and missed auditing Study 3004. Due to the ongoing COVID-19 situation and that all the five completed sites were in compliance, the OSI team requested and the Clinical team agreed to forgo this remaining inspection.

The OSI review team has concluded that "*based on the results of these CI inspections, Study*

RVT-901-3003 and RVT-901-3004 appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication." For details, refer to the OSI review date October 8, 2020 in DARRTS.

Reviewer Comments: ***Concur with the OSI review team's assessments that the data from Studies 3003 and 3004 appear adequate to support the indication.***

4.2. Product Quality

There is an issue of tablet coating color change. Awaiting final CMC review of manufacturer's report, including additional stability data, submitted in November. Pending final CMC review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/ toxicology team's review noted that vibegron was tested up to 9 months in monkeys and 6 months in rats. The monkey was shown to be pharmacologically similar in β3-AR activity compared to humans, while agonist activity at the rabbit and dog β3 adrenergic receptors was approximately 10-fold less potent, and activity at the rat receptor was 100-fold less potent than in humans.

Metabolite profiles in toxicology species were similar to those observed in humans.

No histopathological effects were observed in monkeys up to approximately 75 times the expected clinical exposure at the maximum recommended human dose (MRHD) of 75 mg vibegron (via AUC), except for slight accumulation of brown fat in white adipose tissue (a pharmacologic effect common to beta-3-adrenergic agonists in animals) and very slight cellular infiltration in the liver. A no effect level (NOEL) was observed at 25 mg/kg/day (6-fold Cmax, 2.1-fold AUC), based on ECG effects.

In rats, a no-adverse-effect level (NOAEL) was observed at about 21.3-fold the MRHD. Some brown fat accumulation was observed at this level of administration in male rats. At about 102-fold, one male was found dead in study week 12, and very slight or slight increases in alkaline phosphatase were observed. No other significant toxicities were observed.

No mutagenesis, carcinogenesis, or reproductive toxicity effects were noted and no significant issues identified. The pharm/tox team recommended approval of vibegron 75 mg for the treatment of OAB. See Pharm/tox team's review in DARRTS dated October 20, 2020 for details.

Reviewer Comments: ***Concur with pharm/tox team's review that no significant pharm/tox***

issues were identified.

4.5. Clinical Pharmacology

The following items were submitted and reviewed by ClinPharm: DDI Studies, QT study with IRT consult; effects on vital signs (VS); effect of weight class; antihypertensive and ketoconazole interaction studies.

No significant issues were identified. The ClinPharm team recommended approval of vibegron for the treatment of OAB pending final agreement on product labeling. See ClinPharm team's review in DARRTS dated October 23, 2020 for details.

Reviewer Comments: ***Concur with clinpharm team's assessment.***

4.6. Devices and Companion Diagnostic Issues

Not Applicable

4.7. Consumer Study Reviews

Not Applicable

5. Sources of Clinical Data and Review Strategy

5.1.Table of Clinical Studies

Table 3: Listing of Clinical Trials Relevant to this NDA

Study No. NCT No. Phase; Sponsor/Region	Design; Population	Vibegron Regimen Evaluated	Number of Subjects Treated			
			Vibegron	Comparator	Placebo	Total
Pivotal Efficacy Studies						

Study 3003 NCT03492281 Phase 3; Urovant; Global	Double-blind, randomized, placebo- and active-controlled, multicenter parallel- group 12-week study; following a 2- week placebo run-in period, subjects were randomized 5:5:4 to receive blinded treatment of vibegron, placebo, or tolterodine, respectively Adults with OAB	Vibegron 75 mg, placebo, or tolterodine ER 4 mg administered orally once daily for 12 weeks	545	430	540	1515
Study 3004 NCT03583372 Phase 3; Urovant; US	Double-blind, randomized, active- controlled, 40-week extension study for subjects who completed Study 3003; subjects randomized to vibegron or tolterodine in Study 3003 continued same blinded treatment; those randomized to placebo were randomized 1:1 to receive blinded vibegron or tolterodine Completers from Study 3003	Vibegron 75 mg or tolterodine ER 4 mg, administered orally once daily for 40 weeks	273[a]	232[a]	-[a]	505[a]
Supportive Efficacy and Safety Studies						
Study 008 NCT01314872 Phase 2; Merck; Global	Double-blind, randomized, placebo- and active comparator (tolterodine)-controlled, 2-part efficacy and safety study with 52-week extension Adults with OAB	Part 1: vibegron 3 mg, 15 mg, 50 mg, or 100 mg, tolterodine ER 4 mg, or placebo once daily for 8 weeks; or vibegron 50 mg + tolterodine ER x 4 weeks followed by 50 mg alone x 4 weeks once daily Part 2: vibegron 100 mg, tolterodine ER 4 mg, vibegron 100 mg + tolterodine ER 4 mg, or placebo, once daily x 4 weeks Extension: vibegron 50 mg, vibegron 100 mg, vibegron 100 mg + tolterodine ER 4 mg, or tolterodine ER 4 mg	Base: 931 Extension 605 [b]	Base: 257 Extension: 240 [b]	Base: 205	Base: 1393 Extension 845 [b]

Study 301 No NCT number Phase 3; Kyorin; Japan	Phase 3, randomized, double-blind, placebo-controlled 12-week study; Adults with OAB	Vibegron 50 mg (once daily) + placebo; or vibegron 100 mg (once daily) + placebo; or placebo; or imidafenacin 0.2 mg (twice daily) + placebo; orally 12 weeks	739	117	369	1225
Study 302 No NCT number Phase 3; Kyorin; Japan	Phase 3, open-label, long-term safety and efficacy study; Adults (18 to 75 years of age) with OAB	Vibegron 50 mg (once daily) for 8 weeks, then either vibegron 50 mg or 100 mg (once daily) for 44 weeks	167	-	-	167

ER = extended release; NA = not applicable; OAB = overactive bladder;
a 183 subjects (92 randomized to vibegron; 91 randomized to tolterodine ER) were assigned to placebo in Study 3003 and received a total of 40 weeks of vibegron or tolterodine ER; all other subjects received 52 weeks of active study drug (vibegron or tolterodine) combined for Studies 3003/3004
b 124 subjects (45 randomized to vibegron 50 mg or 100 mg; 79 randomized to comparator) were assigned to placebo in the base study of 008.)
Source: Sponsor Table SCE with Reviewer Edits

5.2. Review Strategy

Efficacy and safety were studied in three Phase 2b studies and one Phase 3 study (at the to-be-marketed dose of 75mg), Study 3003, and its accompanying safety extension Study 3004.

The three Phase 2 and 3 studies (Merck Study 008, Kyorin Study 301 and its extension study Kyorin Study 302) provide support for the primary Phase 3 study but are not considered for primary efficacy as they had different study designs, different endpoints, different dosages (50 mg and 100 mg), different patient populations (Japanese patients in Studies 301 and 302), and different study durations (8 weeks in Merck Study 008 versus 12 weeks in Study 3003, the main Phase 3 study).

The PRO Evidence Dossier which the Sponsor developed to support key efficacy analyses results, including analysis for “clinical meaningfulness”, from both Urovant study 3003 and Merck study 008 was reviewed in consultation with the Clinical Outcomes Assessment (COA) team in the Division of Clinical Outcomes Assessment (DCOA).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1.RVT-901-3003; An International Phase 3, Randomized, Double-Blind,

Placebo- and Active (Tolterodine)-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder

6.1.1. Study Design

Overview and Objective
Urovant conducted Study 3003: (N = 1515): pivotal phase 3 study to evaluate 12-week administration of the 75-mg dose of vibegron compared to placebo with an active comparator, tolterodine extended release (ER) 4 mg.

Objectives:

- Primary Efficacy: To evaluate the efficacy of vibegron 75 mg compared to placebo in subjects with symptoms of OAB, specifically the frequency of micturitions and frequency of urge urinary incontinence (UUI) episodes
- Secondary Efficacy: To evaluate the overall efficacy of vibegron compared to placebo in subjects with symptoms of OAB
- Safety: To evaluate the safety and tolerability of treatment with vibegron;
- Pharmacokinetic: To evaluate the pharmacokinetic (PK) profile of vibegron in subjects with symptoms of OAB
- Exploratory: To evaluate the effect of vibegron compared with placebo in subjects with symptoms of OAB on subject-perceived outcomes

Trial Design
This was an international, Phase 3, randomized, double-blind, placebo-controlled and active controlled (tolterodine), parallel-group, multicenter study to evaluate the safety and efficacy of vibegron 75 mg in men and women patients with symptoms of OAB with approximately 1,400 patients planned to be enrolled at approximately 330 study sites.

At baseline, subjects who met all eligibility criteria were randomized 5:5:4 to receive either vibegron 75 mg, placebo, or tolterodine extended release (ER) 4 mg in a double-blind fashion. For the randomized Treatment Period, subjects were to attend visits at baseline, Week 4, Week 8, and Week 12.

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 subjects who did not enroll in the optional extension study).

Subject-completed bladder diaries and questionnaires were used in all the studies to collect information on OAB symptoms. To minimize the placebo effect and to reduce compliance issues with study drug and study procedures (e.g., diary completion), Studies 3003, included a single-blinded placebo run-in period. Subjects were required to meet entry criteria at

the time of randomization in addition to at screening.

Subjects who completed the Week 12 Visit may have been eligible to enroll in the 40-week double-blind extension study RVT-901-3004 (conducted under a separate protocol) until enrollment of approximately 500 subjects into that extension study was achieved. Subjects who did not enroll into the optional extension study were to have a Follow-up Visit approximately 28 days after the subject's last dose of study treatment (ie. at Week 16 for subjects who completed the Week 12 Visit, or approximately 4 weeks after withdrawal for subjects who discontinued the study early). Additionally, Unscheduled Visit(s) were arranged for subjects with study-related safety concerns, etc. as needed.

Diagnosis and Main Criteria for Eligibility

Key inclusion criteria included the following:

- Having a history of OAB (defined as urgency, with or without UUI, usually associated with frequency and nocturia) for at least 3 months prior to the Screening Visit
- Meeting OAB Wet criteria or OAB Dry criteria (up to 25% of subjects meeting OAB Dry criteria were allowed), based on the Patient Voiding Diary
  - OAB Wet criteria:
    - An average of ≥ 8.0 micturitions per Diary Day*; and
    - An average of ≥ 1.0 UUI episodes per Diary Day; and
    - 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
  - OAB Dry criteria:
    - An average of ≥ 8.0 micturitions per Diary Day; and
    - An average of ≥ 3.0 urgency episodes per Diary Day; and
    - An average of < 1.0 UUI episodes per Diary Day; and
    - 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.

  *Note: A Diary Day was defined as the time between when the subject got up for the day each morning and the time the subject got up for the day the next morning as recorded in the Patient Voiding Diary

Key exclusionary criteria included the following:

- History of 24-hour urine volume greater than 3,000 mL in the past 6 months, or a Urine Volume Diary day measurement greater than 3,000 mL during the Run-in Period
- Lower urinary tract pathology that could be responsible for urgency, frequency, or incontinence
- History of surgery to correct stress urinary incontinence, pelvic organ prolapse, or

procedural treatments for benign prostatic hypertrophy (BPH) within 6 months of Screening
- Had a current history or evidence of Stage 2 or greater pelvic organ prolapse (prolapse extending beyond the hymenal ring)
- Was currently using a pessary for the treatment of pelvic organ prolapse
- Had a known history of elevated post-void residual volume defined as greater than 150 mL
- Underwent bladder training or electrostimulation within 28 days prior to Screening or planned to initiate either during the study
- Had active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or laboratory criteria
- Had a requirement for an indwelling catheter or intermittent catheterization
- Received an intradetrusor injection of botulinum toxin within 9 months prior to Screening.

Duration of Treatment
Subjects in this study were to receive study treatment (vibegron, tolterodine ER, or placebo) for 12 weeks.

Dose Rationale
The Sponsor determined that prior clinical and non-clinical data support selection of vibegron 75 mg administered once daily in patients with OAB and noted that several lines of evidence supported this dosage. The Sponsor stated the following reasons for the selection of a single 75mg daily dose for OAB:

1) higher doses, up to 100 mg for 52 weeks, were studied in Study 008 (see section 6.3), and two Phase 3 studies (Study 301 (see section 6.4) and Study 302 (see section 6.5)

2) Study 008 (see section 6.3) demonstrated dose-dependent efficacy across multiple clinical endpoints in OAB patients with the maximal effect generally estimated between 50 and 100 mg; 75 mg daily dose of vibegron would be expected to capture approximately 90% of the efficacy of 100 mg dose.

3) Slight increases in mean maximum heart rate and infrequent increases in systolic or diastolic blood pressure in patients with OAB were difficult to detect relative to placebo and were not readily distinguishable between 50 and 100 mg of vibegron; these effects appear similar to, or less than, marketed agents tolterodine ER 4 mg and mirabegron 50 mg

4) Vibegron exhibits greater than dose-proportional increases in exposures with mean Cmax increasing ~4-fold when dose increases from 50 to 100 mg. A simulated dose

of 75 mg decreases Cmax by approximately 40% and reduces extremes of exposure compared to 100 mg. From the simulated dose predictions, the Sponsor postulated that lowering Cmax would be expected to maximize the benefit-risk profile for patients with OAB by minimizing the potential for heart rate or blood pressure increases.

Placebo Use
In recognition of the large placebo responses commonly observed in OAB studies, the Sponsor reported that a placebo arm was included based on the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence ((EMA) December 2002).

Active Control
Tolterodine ER, 4mg once daily (OD) orally, an antimuscarinic approved for the treatment of overactive bladder, was an active control for this study.

Study Endpoints
Co-Primary Efficacy Endpoints:

- 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

Key Secondary Efficacy Endpoints:

- 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 (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 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

Additional Secondary Efficacy Endpoints:

- CFB at Week 12 in Health-related Quality of Life (HRQL) Total Score from the OAB-q LF

(1-week recall) in all OAB patients
- CFB at Week 12 in Symptom Bother Score from the OAB-q-LF (1-week recall) in all OAB patients
- Percent of all OAB patients with average number of micturitions < 8 per 24 hours at Week 12
- Percent of OAB Wet patients with at least a 50% reduction from baseline in total incontinence episodes per 24 hours at Week 12
- CFB at Week 12 in overall bladder symptoms based on Patient Global Impression of Severity (PGI-Severity) in all OAB patients
- CFB at Week 12 in overall control over bladder symptoms based on Patient Global Impression of Control (PGI-Control) in all OAB patients

Statistical Analysis Plan

For the analysis of the co-primary endpoints (change from baseline in average number of daily micturitions at Week 12 and change from baseline in average number of daily UUI episodes at Week 12), a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation was planned. The analysis model for each efficacy endpoint would include terms for treatment, visit, OAB Type (Wet vs Dry), Sex (Female vs Male), Region (US vs Rest of World), baseline score, and interaction of visit by treatment. An unstructured covariance matrix was planned to be used to model the correlation among repeated measurements. The Kenward-Roger adjustment was planned to be used with restricted (or residual) maximum likelihood (REML) to make statistical inference.

Other change from baseline endpoints was planned to be analyzed using the same MMRM model.

Response efficacy endpoints planned were the following with analyses using the Cochran-Mantel-Haenszel risk difference estimate:

- proportion of patients with at least 75% reduction or 100% reduction in the average number of daily UUI episodes at Week 12
- proportion of patients with at least 50% reduction in the average number of daily urgency episodes at Week 12

Missing Week 12 data was planned to be analyzed using multiple imputation. For each imputed dataset, the estimated difference in the proportion of responders and 95% confidence interval for the difference would be calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by OAB Type (Wet vs Dry) and Sex (Female vs Male), with weights proposed by Greenland and Robins.

Multiplicity Adjustment

The key secondary endpoints were planned to be tested using a hierarchical testing strategy

using two-sided tests with a = 0.05. No adjustment for multiplicity was determined to be needed.

Power and Sample Size Calculations
Approximately 1,400 patients were planned to be randomized in a 5:5:4 ratio to receive one of the following Study Treatments:

- Vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule (N = 500)
- Placebo tablet to match vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule (N = 500)
- Tolterodine ER 4 mg capsule + placebo tablet to match vibegron 75 mg tablet (N = 400)

Assuming a total of 10% patients would discontinue prior to Week 12 (for any reason), there would be approximately 450 evaluable patients in the vibegron and placebo treatment groups at the end of Week 12. Assuming 75% of the population will have OAB Wet, there would be approximately 337 evaluable patients in the vibegron and placebo treatment groups for the incontinence endpoints. The study would have:

- Approximately 98% power to detect a true underlying between- group treatment difference of 0.6 in change from baseline in micturitions at a two-sided 0.05 level assuming a variability estimate of 2.20 based on vibegron Study 008 data.
- Approximately 98% power to detect a true underlying between- group treatment difference of 0.51 in change from baseline in UUI episodes at a two-sided 0.05 level assuming a variability estimate of 1.68 based on vibegron Study 008 data.

Assuming that these endpoints were uncorrelated, then this study would have 96% power to reject both co-primary hypotheses.

Protocol Amendments
The Sponsor has made two protocol amendments and conducted the study 3003 under RVT-901-3003 Version 3.0. The following table identifies major changes during each amendment:

Table 4: Protocol 3003 Major Amendment Changes

Amendment Version	Protocol Changes
2.0	Efficacy Response Rate: Increase response efficacy endpoint from 70% to 75%, i.e. Percent of OAB Wet patients with a 75% reduction from baseline in UUI episodes per 24 hours at Week 12

3.0	Key Secondary Efficacy Endpoint Changes: Add key secondary efficacy endpoint: ➢ Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12 Remove key secondary efficacy endpoints*: 1) CFB at Week 4 in average number of daily micturitions in all OAB patients 2) CFB at Week 4 in average number of daily UUI episodes in OAB Wet patients 3) CFB to Week 2 in average number of micturitions per 24 hours in all OAB patients 4) CFB to Week 2 in average number of UUI episodes per 24 hours in OAB Wet patients
3.0	Additional Secondary Endpoint Changes: Remove additional secondary endpoint 5) Percent of OAB Wet patients with zero UUI episodes at Week 12
3.0	Exploratory endpoints changes: Added: • Percent of OAB Wet patients with a 100% reduction from baseline in UUI episodes per 24 hours at Weeks 2, 4, and 8 • Percent of all OAB patients with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Weeks 2, 4, and 8 • Percent of all OAB patients with average number of micturitions < 8 per 24 hours at Weeks 2, 4, and 8 • Percent of OAB Wet patients with at least a 50% reduction from baseline in total incontinence episodes per 24 hours at Weeks 2, 4, and 8 • CFB at Weeks 2, 4, and 8 in average number of daily micturitions in all OAB patients • CFB at Weeks 2, 4, and 8 in average number of daily UUI episodes in OAB Wet patients • CFB at Weeks 2, 4, and 8 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB patients • CFB at Weeks 2, 4, and 8 in average number of total incontinence episodes over 24 hours in OAB Wet patients • CFB at Weeks 2, 4, 8, and 12 in number of Nighttime UUI for all OAB Wet patients with at least 1 Nighttime UUI at baseline • Examination of the correlation between diary endpoints and PGI questions Removed:

	• CFB in percent of dry Diary Days (zero UUI episodes) at Week 12 and Week 4 in OAB Wet patients • CFB at Week 12 in average number of nighttime voids for patients with nocturia at baseline

*Removed key secondary endpoints were moved to and combined with exploratory endpoints
Source: Reviewer created Table

6.1.2. Study Results

Compliance with Good Clinical Practices

The Sponsor stated in the CSR that this study was conducted in conformance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICYH) Good Clinical Practice. Quality checks were performed on approximately 5% of the voiding diaries of randomized subjects. Per the Sponsor, all investigators and responsible study site staff attended an investigator training meeting and/or separate study site initiation visit to review study protocol procedures, study requirements, and GCP responsibilities. Principal Investigators signed the investigator page of the protocol to confirm their commitment to conduct the study in accord with the protocol and GCP.

Financial Disclosure

The Sponsor included a financial disclosure and no concerns were raised for this study as no investigator had a financial disclosure.

Patient Disposition

A total of 3149 subjects were screened for this study, of which 1836 entered the Run-in Period; 1518 subjects were subsequently randomized and, of these, 1515 were treated with at least 1 dose of double-blind study drug. A total of 547 subjects were randomized to the vibegron group, 540 to the placebo group, and 431 to the tolterodine group.

The Sponsor noted that during conduct of the study, 19 patients were discovered to have participated in the study at more than one study site. For these patients, all analysis sets removed these cases except in the screened set. The following table summarizes patient disposition in Study 3003:

Table 5: Patient Disposition in Study 3003- Randomized Set

	Placebo N = 540 n (%)	Vibegron 75 mg N = 547 n (%)	Tolterodine ER 4 mg N = 431 n (%)	Overall N = 1518 n (%)

Randomized	540 (100)	547 (100)	431 (100)	1518 (100)
Took at least one dose of double-blind medication	540 (100)	545 (99.6)	430 (99.8)	1515 (99.8)
Completed the study	486 (90.0)	502 (91.8)	385 (89.3)	1373 (90.4)
Discontinued from the study	54 (10.0)	45 (8.2)	46 (10.7)	145 (9.6)
Withdrew consent	21 (3.9)	14 (2.6)	13 (3.0)	48 (3.2)
Lost to follow-up	14 (2.6)	15 (2.7)	10 (2.3)	39 (2.6)
Adverse event	6 (1.1)	8 (1.5)	13 (3.0)	27 (1.8)
Other	8 (1.5)	6 (1.1)	3 (0.7)	17 (1.1)
Lack of efficacy	3 (0.6)	0	1 (0.2)	4 (0.3)
Subject withdrawn due to	1 (0.2)	0	3 (0.7)	4 (0.3)
Protocol deviation	0	2 (0.4)	1 (0.2)	3 (0.2)
Subject withdrawn due to	1 (0.2)	0	1 (0.2)	2 (0.1)
Death	0	0	1 (0.2)	1 (0.1)
Source: CSR: Table 14.1.1.3 with Reviewer Edits				

Protocol Violations/Deviations

The Sponsor reported that deviations were classified as "major" and "minor" during the study where a major protocol deviation has impact on subject safety, alters risks to patients, affects the integrity of study data or influences the conduct of the study. These major deviation patients were excluded from efficacy analysis. The following table summarizes the major protocol deviations in the FAS patient population:

Table 6: Summary of Major Protocol Deviations, Safety and Efficacy- FAS Study 3003

Major Protocol Deviation	**Placebo N = 520 n (%)**	**Vibegron 75 mg N = 526 n (%)**	**Tolterodine ER 4 mg N = 417 n (%)**	**Overall N = 1463 n (%)**
Subjects with at Least One Major Protocol Deviation	**55 (10.6)**	**60 (11.4)**	**46 (11.0)**	**161 (11.0)**
Efficacy	34 (6.5)	47 (8.9)	26 (6.2)	107 (7.3)

Efficacy, Duplicate Patient	2 (0.4)	1 (0.2)	3 (0.7)	6 (0.4)
Safety and Efficacy	2 (0.4)	4 (0.8)	3 (0.7)	9 (0.6)
Safety	20 (3.8)	13 (2.5)	11 (2.6)	44 (3.0)
Other	4 (0.8)	3 (0.6)	5 (1.2)	12 (0.8)
Subjects with at Least One Major Efficacy-Related Protocol Deviation[a]	**37 (7.1)**	**50 (9.5)**	**31 (7.4)**	**118 (8.1)**
Derived Investigational Product (IP) Compliance*	15 (2.9)	16 (3.0)	12 (2.9)	43 (2.9)
Inclusion Criteria	7 (1.3)	17 (3.2)	8 (1.9)	32 (2.2)
Exclusion Criteria	7 (1.3)	8 (1.5)	7 (1.7)	22 (1.5)
Procedure Not Per Protocol	5 (1.0)	7 (1.3)	3 (0.7)	15 (1.0)
Concomitant Medication	4 (0.8)	3 (0.6)	2 (0.5)	9 (0.6)
Other	3 (0.6)	3 (0.6)	2 (0.5)	8 (0.5)
Visit Out of Window	1 (0.2)	3 (0.6)	2 (0.5)	6 (0.4)
Missed Study Visit	0	1 (0.2)	0	1 (0.1)

Note: A subject may be included in more than one category of major PD.
[a] Efficacy-related deviations included the classifications of "Efficacy", "Efficacy, Duplicate Patient", and "Safety and Efficacy"
**Derived IP Compliance category not further specified in the CSR*
Source: Study 3003 CSR Table 14.1.2.1

Table of Demographic Characteristics

The demographic and baseline characteristics for Study 3003 showed balance between treatment groups to age, gender, race, and region.

The study population was generally older, with a mean age of 60.2 years and 42.9% of subjects ≥ 65 years of age at baseline. The following table summarizes the demographics and other baseline characteristics of the full analysis set (FAS):

Table 7: Summary Patient Demographic and Baseline Characteristics (FAS) Study 3003

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417	Overall N = 1463
Age (years), mean (SD)	59.9 (13.33)	60.8 (13.30)	59.8 (13.19)	60.2 (13.28)
Age category (years), n (%)				
< 40	45 (8.7)	40 (7.6)	36 (8.6)	121 (8.3)
≥ 40 to < 55	111 (21.3)	112 (21.3)	95 (22.8)	318 (21.7)
≥ 55 to < 65	144 (27.7)	132 (25.1)	120 (28.8)	396 (27.1)
≥ 65 to < 75	163 (31.3)	167 (31.7)	119 (28.5)	449 (30.7)
≥ 75	57 (11.0)	75 (14.3)	47 (11.3)	179 (12.2)
Sex, n (%)				
Male	75 (14.4)	77 (14.6)	65 (15.6)	217 (14.8)
Female	445 (85.6)	449 (85.4)	352 (84.4)	1246 (85.2)
Race, n (%)				
American Indian or Alaska Native	3 (0.6)	1 (0.2)	0	4 (0.3)
Asian	29 (5.6)	27 (5.1)	26 (6.2)	82 (5.6)
Black or African American	79 (15.2)	74 (14.1)	69 (16.5)	222 (15.2)
White	406 (78.1)	422 (80.2)	317 (76.0)	1145 (78.3)
Other	3 (0.6)	2 (0.4)	5 (1.2)	10 (0.7)
Region, n (%)				
US	463 (89.0)	472 (89.7)	376 (90.2)	1311 (89.6)
Non-US	57 (11.0)	54 (10.3)	41 (9.8)	152 (10.4)

Source: CSR Table 14.1.3.1.2 with reviewer edits

<u>Reviewer comments:</u> The Sponsor did not report ethnicity or Native Hawaiian or Pacific Islander groups in the demographics report. 89%-90% of the patients were US patients so that the study is reflective of the US population. The older patient population is consistent with the OAB patient population. The study protocol recruited 75 male patients (14.4%) in line with the study protocol that restricted male enrollment to < 15%.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

OAB and other OAB medication use:

Other baseline OAB characteristics showed balance between OAB types, Dry and Wet, prior anticholinergic use in past 12 months, and prior β-agonist use between randomized treatment groups. The following table summarizes the patients' OAB characteristics within each randomized treatment group.

Table 8: OAB Baseline Characteristics By Treatment Group (FAS)-Study 3003

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417	Overall N = 1463
OAB type, n (%)				
Wet	405 (77.9)	403 (76.6)	319 (76.5)	1127 (77.0)
Dry	115 (22.1)	123 (23.4)	98 (23.5)	336 (23.0)
Prior anticholinergic use in the last 12 months, n (%)				
Yes	85 (16.3)	77 (14.6)	51 (12.2)	213 (14.6)
Prior beta-3 agonist use in the last 12 months, n (%)				
Yes	27 (5.2)	21 (4.0)	32 (7.7)	80 (5.5)

Source: CSR Table 14.1.3.1.2 with Reviewer Edits

Males and BPH Status in Study:
For the subgroup of male subjects (n = 217), a slightly higher proportion of subjects in the vibegron and tolterodine treatment groups entered the study with BPH compared with subjects in the placebo group.

Table 9: Baseline BPH Status Males (FAS) Study 3003

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417	Overall N = 1463
Male (% overall pts)	75 (14.4)	77 (14.6)	65 (15.6)	217 (14.8)
Benign prostate hyperplasia, yes (male only), n (% of males)	16 (21.3)	29 (37.7)	22 (33.8)	67 (30.9)

Source: CSR Table 14.1.3.1.2 with Reviewer Edits

***Reviewer Comments:* Although randomization was 5:5:4 (vibegron: tolterodine: placebo), there was still a slight inbalance of male patients randomized to vibegron (n=77, 37.7%) and tolterodine (n=65, 33.8%) compared to placebo (n=75, 21.3%) which was likely related to the small number of male patients allowed in the study which was capped at 15% of the overall patients.**

OAB Baseline Characteristics
The following table summarizes patients' baseline OAB characteristics, compared within treatment groups in the FAS.

Table 10: Baseline OAB Characteristics By Treatment Group in FAS Study 3003

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417	Overall N = 1463
Micturitions[a]				
n	520	526	417	1463
Mean (SD)	11.75 (4.007)	11.31 (3.420)	11.48 (3.153)	11.51 (3.573)
Median	10.43	10.43	10.67	10.57
Q1, Q3	9.15, 13.14	9.00, 12.57	9.13, 12.86	9.13, 12.86
Min, Max	0.1, 30.9	0.0, 30.0	4.1, 24.0	0.0, 30.9
Urge Urinary Incontinence Episodes[a]				
n	520	526	417	1463
Mean (SD)	2.82 (2.994)	2.73 (2.883)	2.72 (2.635)	2.76 (2.854)
Median	2.00	2.00	2.00	2.00
Q1, Q3	1.00, 3.57	0.86, 3.71	1.00, 3.57	1.00, 3.67
Min, Max	0.0, 23.7	0.0, 27.9	0.0, 17.0	0.0, 27.9
Urgency Episodes[a]				
n	520	526	417	1463
Mean (SD)	8.13 (4.668)	8.11 (4.400)	7.92 (3.883)	8.06 (4.357)
Median	8.00	7.75	8.00	7.86
Q1, Q3	4.59, 10.50	4.60, 10.71	4.86, 10.33	4.71, 10.57
Min, Max	0.0, 30.7	0.1, 30.0	0.7, 21.8	0.0, 30.7
Total Incontinence Episodes[a]				
n	520	526	417	1463
Mean (SD)	3.37 (3.713)	3.29 (3.578)	3.24 (3.109)	3.31 (3.499)
Median	2.25	2.14	2.29	2.25
Q1, Q3	1.13, 4.46	1.00, 4.43	1.14, 4.57	1.00, 4.50
Min, Max	0.0, 30.5	0.0, 28.4	0.0, 20.4	0.0, 30.5
Voided Volume per Micturition[b]				
n	514	524	415	1453

Mean (SD)	148.3 (60.67)	155.4 (63.07)	147.0 (60.79)	150.5 (61.65)
Median	141.7	150.0	143.3	144.4
Q1, Q3	107.1, 183.9	112.8, 193.4	104.3, 177.8	108.4, 184.3
Min, Max	7, 383	2, 406	18, 356	2, 406

[a] Daily Averages were calculated as the sum of the event type on Complete Diary Days divided by the number of Complete Diary Days
[b] Average volume voided per micturition was calculated as the arithmetic mean of all voids for which a subject recorded the volume.
Source: Table 14.1.3.2.2 with reviewer edits

OAB Incontinence Baseline Characteristics:
OAB Wet patients with baseline incontinence were the majority of patients in the study, 1127 of 1143 patients (77%). The following table summarizes the baseline OAB characteristics of these OAB Wet patients, the FAS-I analysis set.

Table 11: OAB Wet-Incontinence Baseline Characteristics (FAS-I) Study 3003

	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319	Overall N = 1127
Micturitions[a]				
n	405	403	319	1127
Mean (SD)	11.69 (4.074)	11.33 (3.410)	11.45 (3.189)	11.49 (3.606)
Median	10.43	10.43	10.57	10.43
Q1, Q3	9.00, 13.14	9.14, 12.56	9.13, 12.71	9.14, 12.71
Min, Max	0.1, 30.9	2.4, 30.0	4.1, 24.0	0.1, 30.9
Urge Urinary Incontinence Episodes[a]				
n	405	403	319	1127
Mean (SD)	3.49 (3.053)	3.43 (2.894)	3.42 (2.592)	3.45 (2.869)
Median	2.50	2.63	2.43	2.57
Q1, Q3	1.57, 4.43	1.57, 4.14	1.71, 4.57	1.57, 4.43
Min, Max	0.0, 23.7	0.0, 27.9	0.0, 17.0	0.0, 27.9
Urgency Episodes[a]				
n	405	403	319	1127
Mean (SD)	7.99 (4.559)	7.97 (4.389)	7.77 (3.875)	7.92 (4.311)
Median	7.86	7.67	7.86	7.86
Q1, Q3	4.57, 10.29	4.57, 10.57	4.71, 10.14	4.57, 10.29
Min, Max	0.3, 30.7	0.1, 30.0	0.7, 19.7	0.1, 30.7

Total Incontinence Episodes[a]				
n	405	403	319	1127
Mean (SD)	4.17 (3.823)	4.14 (3.631)	4.06 (3.071)	4.13 (3.552)
Median	3.00	3.14	3.00	3.00
Q1, Q3	1.78, 5.00	1.78, 5.29	1.88, 5.40	1.86, 5.29
Min, Max	0.0, 30.5	0.0, 28.4	0.1, 20.4	0.0, 30.5
Voided Volume per Micturition[b]				
n	400	401	318	1119
Mean (SD)	150.8 (59.99)	157.5 (64.21)	146.4 (61.45)	152.0 (62.05)
Median	144.2	150.8	141.3	145.8
Q1, Q3	111.6, 186.3	115.0, 193.7	101.7, 179.3	109.7, 187.5
Min, Max	25, 371	2, 406	18, 356	2, 406

[a] Daily Averages were calculated as the sum of the event type on Complete Diary Days divided by the number of Complete Diary Days
[b] Average volume voided per micturition was calculated as the arithmetic mean of all voids for which a subject recorded the volume.
Source: Table 14.1.3.2.3 with reviewer edits

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance
Overall, high rates of compliance were observed for both tablets and capsules; categorical assessments (< 75%, ≥ 75% to ≤ 125%, or > 125%) demonstrated that < 3% of subjects were included in < 75% compliance category across all treatment groups (SAF and FAS) during the Double-blind Period.

Prior OAB Medications:
There were no notable differences across the treatment groups in the proportion of subjects who reported taking at least 1 prior OAB medication in the last 12 months. There were small differences between the 3 groups in the proportions of subjects who took specific medications; oxybutynin was the most common prior medication taken by subjects in the placebo and vibegron groups, whereas mirabegron was the most common prior medication taken by subjects in the tolterodine group. The following table summarizes OAB medications taken prior to the study.

Table 12: Prior OAB Medication-Last 12 Months (SAF)

	Placebo N = 540 n (%)	Vibegron 75 mg N = 545 n (%)	Tolterodine ER 4 mg N = 430 n (%)	Overall N = 1515 n (%)
At least one prior OAB medication[a]	108 (20.0)	93 (17.1)	77 (17.9)	278 (18.3)
Oxybutynin	35 (6.5)	32 (5.9)	22 (5.1)	89 (5.9)
Mirabegron	27 (5.0)	21 (3.9)	32 (7.4)	80 (5.3)
Solifenacin succinate	25 (4.6)	21 (3.9)	14 (3.3)	60 (4.0)
Oxybutynin hydrochloride	7 (1.3)	10 (1.8)	3 (0.7)	20 (1.3)
Solifenacin	9 (1.7)	6 (1.1)	5 (1.2)	20 (1.3)
Tolterodine	7 (1.3)	8 (1.5)	4 (0.9)	19 (1.3)
Tolterodine L-tartrate	9 (1.7)	4 (0.7)	4 (0.9)	17 (1.1)
Fesoterodine fumarate	2 (0.4)	1 (0.2)	5 (1.2)	8 (0.5)
Trospium chloride	1 (0.2)	2 (0.4)	1 (0.2)	4 (0.3)
Fesoterodine	1 (0.2)	2 (0.4)	0	3 (0.2)
Trospium	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)

[a] Prior medications are defined as medications having taken in the last 12 months and stopped prior to the Run-in Visit.
Source: Table 14.1.4.2 with reviewer edits

Efficacy Results – Co-Primary Endpoints

Efficacy in Study 3003 was measured by two co-primary efficacy endpoints meeting 0.05 for statistical significance:

- average daily number of micturitions CFB at Week 12
- average daily number of UUI episodes CFB at Week 12

Co-Primary Endpoint: Average daily number of micturitions CFB at Week 12:
Treatment with vibegron 75 mg once daily appeared to result in statistically significant reductions from baseline at Week 12 relative to placebo in the average daily number of micturitions (least- squares [LS] mean difference of -0.5, $p < 0.001$). The following table shows results for this co-primary efficacy endpoint, average daily number of micturitions from baseline at Week 12 in Study 3003:

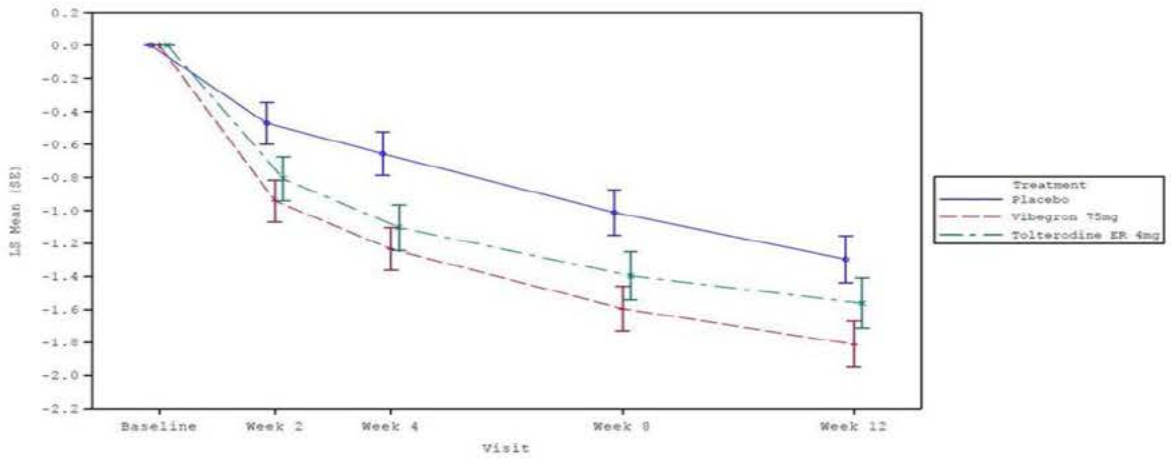
Table 13: Study 3003: Primary Efficacy Analysis: Change from Baseline Average Daily Number Micturitions Week 12 (MMRM)-FAS

	Placebo N=520	Vibegron 75 mg N=526	Tolterodine ER 4 mg N=417
Baseline Average Daily Number of Micturitions			
N	520	526	417
Mean (SD)	11.75 (4.007)	11.31 (3.420)	11.48 (3.153)
Change from Baseline at Week 12 in Average Daily Number of Micturitions			
n	475	492	378
LS means (SE)	-1.3 (0.14)	-1.8 (0.14)	-1.6 (0.15)
95% CI	-1.6 to -1.0	-2.1 to -1.5	-1.9 to -1.3
Active – Placebo			
LS means difference (SE)		-0.5 (0.15)	-0.3 (0.16)
95% CI		-0.8 to -0.2	-0.6 to 0.1
P-value		< 0.001	0.0988

Notes: Covariates included in the mixed model for repeated measures were study visit, OAB type, sex, region, baseline number of micturitions and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
Source: Table 14.2.1.1.2 with reviewer edits

The following figure shows the mean of changes from baseline (CFB) in average daily number of micturitions over the study's duration:

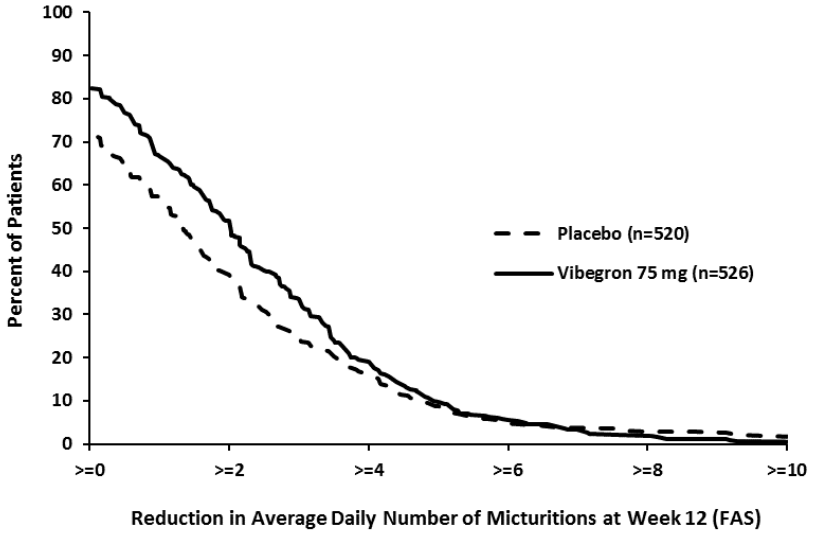
Figure 1: Study 3003: Plot of LS Means (SE) Change from Baseline in Average Daily Number Micturitions (MMRM)



Source: CSR Figure 14.2.1.1.13
Note: LS means (SE) are computed from the MMRM model displayed in Table 14.2.1.1.2.

The following figure illustrates the percentage of patients who experienced >=0, >=2, >=4, >=6, >=8 and >=10 reduction in average daily micturitions at week 12 in Study 3003.

Figure 2: CDF Graph Micturitions Vibegron Placebo Study 3003



Source: Graph provided by FDA primary Biometrics reviewer

Analysis of "Clinical Meaningfulness" for the Micturition Endpoint
The Division of Clinical Outcome Assessments (DCOA) has consulted during the drug development program, giving input on the patient reported outcomes (PROs) and efficacy endpoints.

The COA review team evaluated the patient voiding diary (PVD) for content validity and the Sponsor's proposed thresholds for meaningful within-patient score change. The consult team determined that the PVD has adequate measurement properties but there is uncertainty about the threshold for meaningful within-patient score change. The Sponsor conducted anchor-based methods supplemented with empirical cumulative distribution function (eCDF) and probability density curves to derive the thresholds for "clinically meaningful" within-patient score change for each COA endpoint of urinary frequency, UUI, and urgency. For a detailed information, refer to the COA consult in DARRTS. The COA review team noted the following:

"… the clinically meaningful within-patient change threshold derived from Study 3003 was considerably higher compared with the threshold obtained from Study 008.

— For urinary frequency, a meaningful within-patient score change in average daily number of micturitions appears to fall somewhere in the range of -3.0 to -3.5 based on the anchor-based eCDF curves (using Patient Global Impression

(PGI)-Severity anchor scale from Study 3003 data; patients deemed a 1-category change on the PGI-Severity anchor scale as a meaningful improvement) and -2.7 to -3.0 (using the PGI-Frequency anchor scale from Study 3003 data). Based on Study 3003 data, when you look at the aforementioned ranges, there is minimal separation between the treatment and the placebo arm."

***Reviewer Comments:* Vibegron 75 mg showed statistically significant differences in the co-primary endpoint of average daily micturition reduction, measured by PVD, but the difference over placebo is small (-0.5 episodes).**

In their analysis of the clinical meaningfulness of changes from baseline in the number of events (e.g., micturitions, UUI, etc.), the DCOA team found a clinical meaningful within-patient change threshold for number of micturitions of -3.0 to -3.5 change (based on the PGI-Severity scale) or -2.7 to -3.0 (based on the PGI-Frequency scale) for meaningful improvement. In looking at the CDF graph, provided by Biometrics at a point where DCOA's anchor-based analyses (using the PGI-Severity anchor scale or PGI-Frequency anchor scale) found clinically meaningful improvements (-2.7 to -3.5 change), the separation of the curves between vibegron and placebo is small, which may reflect minimal clinically meaningful improvement for the vibegron group over placebo.

Co-Primary Endpoint: Average daily number of urge urinary incontinence episodes (UUI) CFB at Week 12:

Treatment with vibegron 75 mg once daily appeared to result in statistically significant reductions from baseline at Week 12 relative to placebo in the average daily number of UUI episodes (LS means difference of -0.6, $p < 0.0001$). In the vibegron 75 mg group, reductions in the average daily number of UUI episodes compared to placebo were observed within 2 weeks. The reductions were maintained over the duration of the study (12 weeks). The following table shows results for this co-primary efficacy endpoint, average daily number of UUI from baseline at Week 12 in Study 3003.

Table 14: Study 3003: Primary Efficacy Analysis (MMRM): Change from Baseline in Average Daily Number of UUI Episodes Week 12 FAS-I

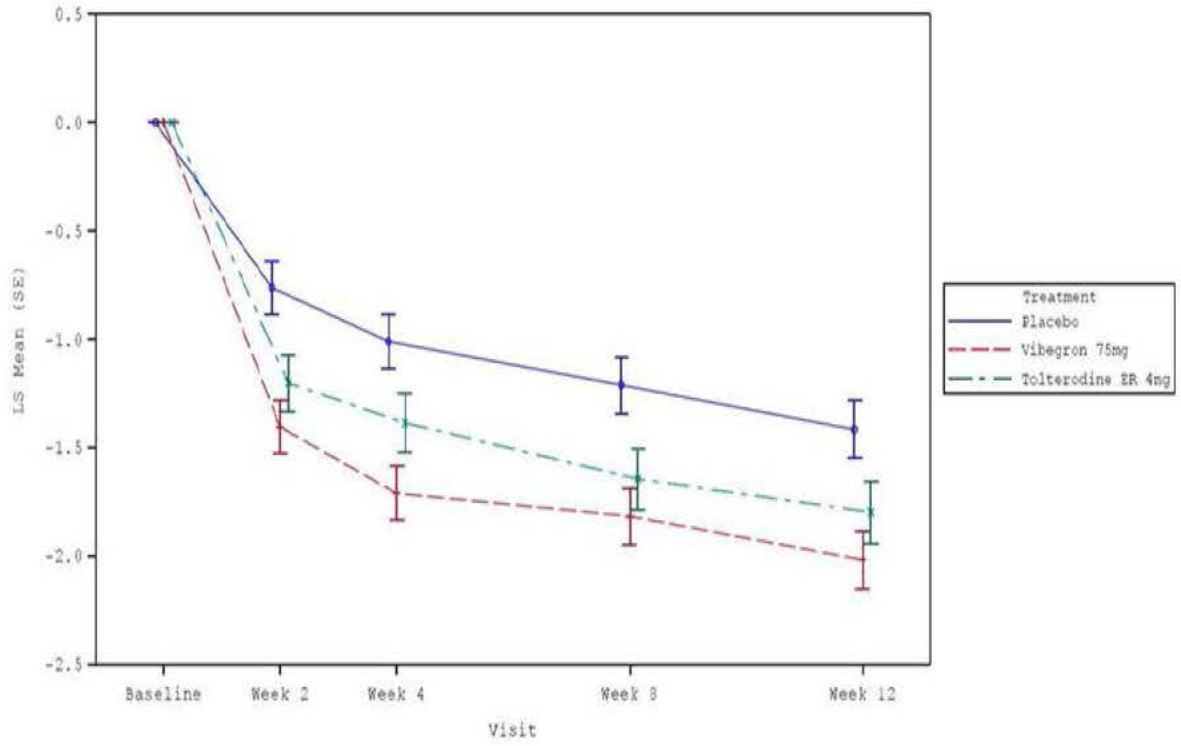
	Placebo N=405	Vibegron 75 mg N=403	Tolterodine ER 4 mg N=319
Baseline Average Daily Number of UUI Episodes			
N	405	403	319
Mean (SD)	3.49 (3.053)	3.43 (2.894)	3.42 (2.592)
Change from Baseline at Week 12 in Average Daily Number of UUI Episodes			
N	372	383	286

LS means (SE)	-1.4 (0.13)	-2.0 (0.13)	-1.8 (0.14)
95% CI	-1.7 to -1.2	-2.3 to -1.8	-2.1 to -1.5
Active – Placebo			
LS means difference (SE)		-0.6 (0.14)	-0.4 (0.15)
95% CI		-0.9 to -0.3	-0.7 to -0.1
P-value		< 0.0001	0.0123

Notes: Covariates included in the mixed model for repeated measures were study visit, sex, region, baseline number of UUI episodes and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
Source: Table 14.2.2.1.2 with reviewer edits

The following figure depicts the average daily UUI episodes by treatment arm.

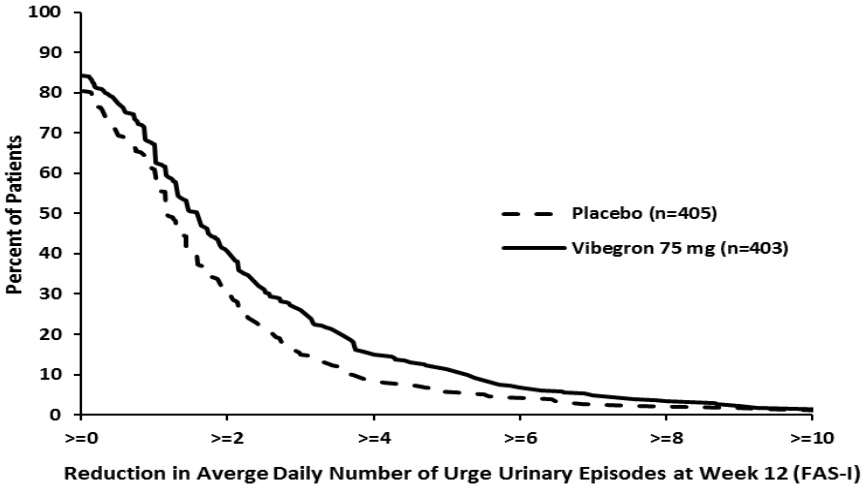
Figure 3: Study 3003: Plot of LS Means (SE) of Change from Baseline in Average Daily Number of UUI Episodes (MMRM)- FAS-I



Note: LS means (SE) were computed from the MMRM model displayed in Table 14.2.2.1.2.
Source: Figure 14.2.2.1.13

The following figure illustrates the percentage of patients who experienced >=0, >=2, >=4, >=6, >=8 and >=10 reduction in average daily number of urge urinary incontinence (UUI) episodes at week 12, comparing vibegron to placebo.

Figure 4: CDF Graph UUI episodes Vibegron Placebo Week 12 Study 3003



Source: Graph provided by FDA primary Biometrics reviewer

In their analysis of "clinically meaningfulness" of the changes from baseline to week 12 in the number of UUI, the DCOA consult team had comments on the Sponsor's proposed clinically meaningful definition of within-patient percent change of ≥ 75% reduction in average daily UUI episodes based on data from the Phase 2B Merck Study 008. The DCOA consult team found that based on their analysis of the Study 3003 data, a clinically meaningful within-patient percent change threshold in average daily UUI episodes appeared to be an 89% to 90% reduction, depending on anchor scale used. Based on that definition of a clinically meaningful within-patient change for UUI, the DCOA team stated:

> *"Based on Study 3003 data, of the 382 patients treated with vibegron, 35.3% had ≥ 90% reduction in the average daily number of UUI episodes at 12 weeks compared to 23.7% of patients (n=371) receiving placebo."*

***Reviewer Comments:* vibegron 75 mg showed statistically significant differences in the co-primary endpoint of average daily UUI episodes, measured by PVD, but the difference over placebo is small (-0.6 episodes).**

In their analysis of "clinical meaningfulness" of the data from Study 3003, DCOA noted a difference between the Sponsor's proposed meaningful within-patient percent change of

average daily UUI reduction (75%), derived from Study 008 data and the results from Study 3003 (90%). The reason for the change from ≥ 75% to ~ 90% reduction from Study 008 to Study 3003 is unknown. Inclusion and exclusion criteria were similar in the two studies, but two notable differences are included in the following table. Also, see the Appendix 13.4 for differences in the PVD between the two studies.

Table 15: Study 008 and 3003 Notable Differences

Notable Differences	Study 008	Study 3003
PVD Changes "urgency"	**Need to Urinate Immediately (Strong Urge)** *(Check if you felt a strong urge or strong need to urinate immediately)"*	**NEED TO URINATE IMMEDIATELY** *(Check if you felt a need to urinate immediately)*
Study Location and Demographics	25% Japanese patients	90% US based patients; 5.6% Asian patients

Source: Reviewer created table from PVD in PRO Dossier

Based on DCOA's anchor-based analyses of the data from Study 3003 to estimate a clinical meaningful within-patient change, it would appear that a 90% reduction from baseline in UUI might be required for patients to consider the treatment clinically meaningful. Such a high threshold for "clinical meaningfulness" may reflect patients' desire for complete continence and that partial continence is unsatisfying.

Responder analyses were carried out for the UUI endpoint. Differences between groups were observed at each strata. Based on the DCOA analysis of "clinical meaningfulness", it would appear that some patients will have clinical meaningful improvements in UUI, but many will not.

For labeling, discussions are still underway as to the type of UUI responder analyses to show (e.g., whether to show CDF graphs, 75% reduction, 90% reduction, 100% reduction, or some combination of these analyses). Based on DCOA's analysis of data from study 3003, their analysis of "clinical meaningfulness" would lend support for a 90% UUI responder analysis as more appropriate than the 75% UUI responder analysis as the DCOA analysis was based on data from study 3003.

Data Quality and Integrity

Potential Data Anomalies:
In CSR Study 3003, section 9.8.3 Changes to Analyses Following Database Lock, the Sponsor noted "potential data anomaly" at two sites, audited those two sites, 10-156 and 27-105, and performed post-hoc sensitivity analyses on the co-primary endpoints, excluding those two sites.

The Sponsor concluded that the sensitivity analysis demonstrated that the endpoints were unchanged with removal of data from the two sites.

In response to the March 4, 2020 filing letter, the Sponsor provided additional information on March 19, 2020 on the issue of "potential data anomaly" to a Biometrics Information Request (IR) with identification of the potential data anomaly(ies) at each site and took steps to resolve the issue.

Reviewer Comments: ***After CRAs reported potential data anomalies at two sites, the Sponsor audited both sites, re-trained staff at site 10-156 for diary completion, and had an independent auditor confirm unique patients. The two sites were the following:***

1) 10-156, also inspected by OSI
2) 27-105

Ling Yang of the Office of Scientific Investigation (OSI) noted that the ORA investigator who inspected site 10-156 did not note any "data anomaly" and the site inspection has been completed without concerns and issued a NAI (by email).

The Sponsor also performed ad-hoc sensitivity analyses, removing the two sites, with results consistent with the co-primary endpoints for the full analysis set. This issue is considered resolved.

Efficacy Results – Secondary and other relevant endpoints

The Sponsor tested each key secondary endpoint sequentially in the order listed in section 6.1.1 key secondary endpoints which showed that vibegron endpoints were statistically significant over placebo for all 7-key secondary OAB endpoints.

Each of the key secondary endpoints are discussed below in order:

Urgency Episodes
At baseline, the average daily number of urgency episodes was similar across the 3 treatment groups. Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant reduction (representing an improvement) from baseline at Week 12 in the adjusted average daily number of urgency episodes as compared with placebo treatment ($p = 0.0020$). Further, treatment with vibegron demonstrated numerically greater decreases in the number of average daily urgency episodes compared with tolterodine treatment.

In the comparison between placebo and tolterodine, the Week 12 decrease from baseline in the adjusted average daily number of urgency episodes did not reach statistical significance.

The following table shows the daily average number of urgency episodes (need to urinate immediately) for vibegron and tolterodine compared to placebo at week 12:

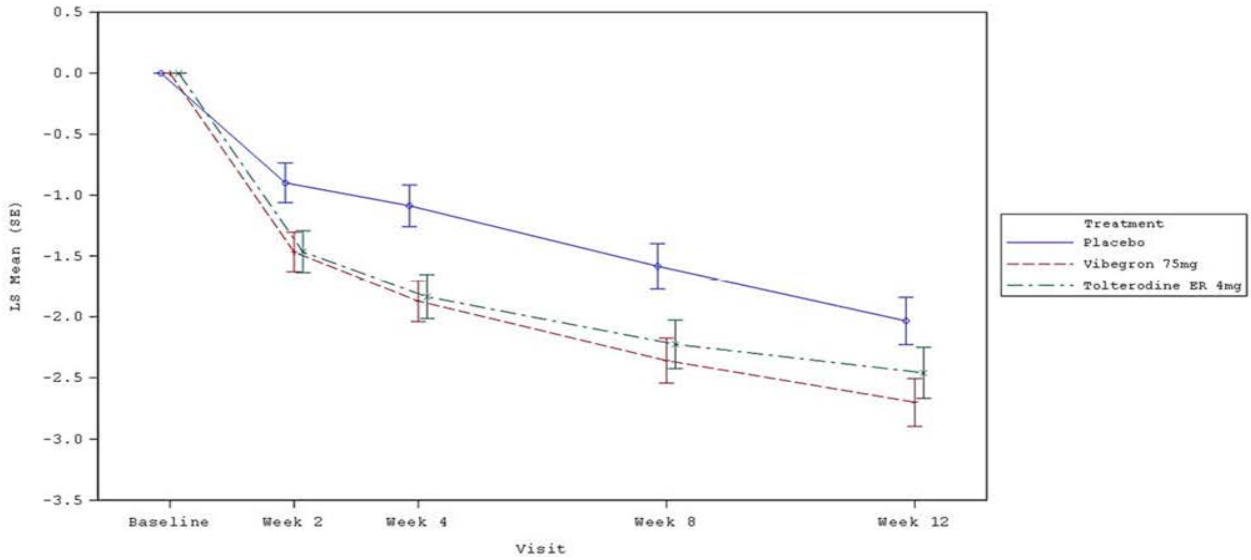
Table 16: Average Daily Urgency Episodes Change from Baseline for Vibegron, Tolterodine, Placebo Week 12 (FAS)

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Baseline			
n	520	526	417
Mean (SD)	8.13 (4.668)	8.11 (4.400)	7.92 (3.883)
Week 12			
n	475	492	378
Mean (SD)	5.76 (4.473)	5.29 (4.500)	5.36 (4.425)
Change from Baseline at Week 12			
n	475	492	378
LS means (SE)	-2.0 (0.19)	-2.7 (0.19)	-2.5 (0.21)
95% CI	-2.4 to -1.7	-3.1 to -2.3	-2.9 to -2.0
Active – Placebo			
LS means difference (SE)		-0.7 (0.22)	-0.4 (0.23)
95% CI		-1.1 to -0.2	-0.9 to 0.0
P-value		0.0020	0.0648

Notes: Covariates included in the mixed model for repeated measures were study visit, OAB type, sex, region, baseline number of urgency episodes, and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
Source: Table 14.2.3.1.2 with reviewer edits

The following figure shows average daily number of urgency episodes, change from baseline in FAS population.

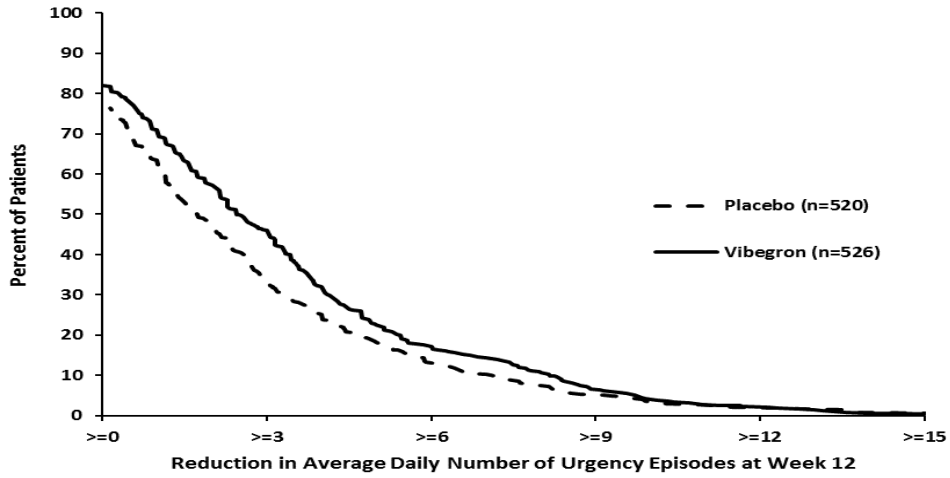
Figure 5: Average Daily Urgency Episodes Change from Baseline -FAS



Notes: Least squares (LS) means (standard error [SE]) were computed from the MMRM model.
P-value (vibegron – placebo): < 0.001 at Week 2, < 0.0001 at Week 4, < 0.001 at Week 8, and 0.0020 at Week 12
P-value (tolterodine ER – placebo): < 0.001 at Week 2, < 0.0001 at Week 4, 0.0027 at Week 8, and 0.0648 at Week 12
Source: Study 3003 CSR, Figure 14.2.3.1.4, Table 14.2.3.1.2

For urgency episodes, the following CDF graph illustrates the percentage of patients who experienced >=0, >=3, >=6, >=9, >=12 and >=15 reduction in average daily number of urgency episodes at week 12 in Study 3003.

Figure 6: CDF Graph Urgency Episodes Vibegron Placebo Week 12 Study 3003



Source: Graph provided by FDA primary Biometrics reviewer

For urgency episodes, the DCOA consult team analyzed the applicant's proposed clinically meaningful within-patient percent change and compared that to the DCOA-calculated clinically meaningful change. Based on the data from study 3003, DCOA found that a ≥ 60% reduction in average daily urgency episodes would be considered meaningful by patients. The DCOA consult team stated the following in their consult:

> *"For urgency episodes, the applicant proposed a meaningful within-patient percent change of ≥50% reduction in average daily urgency episodes based on Study 008 data.*
>
> *However, based on Study 3003 data, a meaningful within-patient percent change threshold in average daily UUI episodes appears to be a ~ -61% reduction based on the anchor-based eCDF curves (using PGI-Severity anchor scale). Based on Study 3003 data, of the 492 patients treated with vibegron, 33.7% had ≥60% reduction in the average daily number of urgency episodes at 12 weeks compared to 28.1% of patients (n=474) receiving placebo."*

Reviewer Comments: ***vibegron 75 mg showed statistically significant differences over placebo in the key secondary endpoint of average daily urgency episodes, measured by PVD, but the difference over placebo is small (-0.7episodes).***

Based on the DCOA team's analyses, the clinical meaningful within-patient reduction was ≥ 60% reduction in average daily urgency episodes in Study 3003, which is higher than the Sponsor's proposal of ≥ 50% which was based on results from Study 008.

The DCOA team's analysis found that 33% of vibegron patients had ≥60% reduction in the average daily number of urgency episodes at 12 weeks compared to 28.1% of patients receiving placebo. The difference of 4.9% of patients who achieve the DCOA-calculated clinical meaningful threshold in Study 3003 is minimal.

Responder analyses were carried out for the urgency (need to urinate immediately) endpoint. Differences were observed at each strata. Based on the DCOA team's analysis of "clinical meaningfulness", it would appear that some patients will have clinical meaningful improvement in urgency, but many will not.

For labeling, urgency should be termed "urgency (need to urinate immediately)" as this was the term presented to patients in the patient voiding diary (PVD) in studies 3003 and 3004.

Urge Urinary Incontinence 75% Responder Analysis

Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant difference from placebo in the percent of OAB Wet subjects with a ≥ 75% reduction from baseline at Week 12 in

average daily number of UUI episodes (adjusted difference from placebo of 16.5%, p < 0.0001).

Compared with tolterodine, treatment with vibegron demonstrated a numerically greater proportion of subjects with a ≥ 75% reduction from baseline in the number of average daily UUI episodes.

The following table summarizes the key secondary endpoint of UUI episodes in OAB Wet patients who reported ≥ 75% reduction from baseline for vibegron and tolterodine:

Table 17: ≥ 75% Reduction Average Daily UUI Episodes in OAB Wet Patients (FAS-I) Week 12

	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319
Subjects with at least 75% reduction in UUI from baseline at Week 12			
Unadjusted n (%)	149 (36.8)	211 (52.4)	152 (47.6)
Adjusted n (%)	133 (32.8)	199 (49.3)	135 (42.2)
Active – Placebo[a]			
CMH Difference		16.5	9.4
95% CI		9.7 to 23.4	2.1 to 16.7
p-value		< 0.0001	0.0120

Notes: MI was used to impute values missing for any reason at the weeks analyzed.
Presented frequencies and the denominator used for percentages were based on subjects in the FAS-I and randomized treatment.
a The difference in proportion and corresponding CI and p-value was calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by sex (female vs male), with weights proposed by Greenland and Robins.
Source: Table 14.2.4.1.1 with reviewer edits

<u>Reviewer Comments:</u> As discussed in the UUI co-primary endpoint section above, the Sponsor proposed the 75% reduction in UUI from baseline endpoint as a pre-defined secondary endpoint in Study 3003 based on data from Study 008 but the DCOA team's anchor-based analysis of data from Study 3003 determined a higher threshold for clinically meaningful within-patient reductions (~ 90% reduction from baseline). The appropriate way to show responder analyses in final labeling for Study 3003 remains under discussion.

Urge Urinary Incontinence 100% Responder Analysis

Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant difference from placebo in the percent of OAB Wet subjects with a 100% reduction from baseline at Week 12 in average daily number of UUI episodes (adjusted difference from placebo of 6.3%, p = 0.0360). Compared with tolterodine, vibegron demonstrated a numerically greater proportion of subjects with a 100% reduction from baseline in the number of average daily UUI episodes.

For placebo-adjusted tolterodine treatment, the percentage of subjects with a 100% reduction from baseline in average daily number of UUI episodes did not reach statistical significance at week 12.

The following table shows the 100% UUI responder analysis for vibegron and tolterodine treatment at week 12 for OAB Wet patients.

Table 18: UUI 100% Responder Analysis Week 12 (FAS-I)

	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319
Subjects with 100% reduction in UUI from baseline at Week 12			
Unadjusted n (%)	91 (22.5)	116 (28.8)	85 (26.6)
Adjusted n (%)	77 (19.0)	102 (25.3)	67 (20.9)
Active – Placebo[a]			
CMH Difference		6.3	1.9
95% CI		0.4 to 12.1	-4.1 to 7.8
p-value		0.0360	0.5447

Notes: MI was used to impute values missing for any reason at the weeks analyzed.
Presented frequencies and the denominator used for percentages were based on subjects in the FAS-I and randomized treatment.
a The difference in proportion and corresponding CI and p-value was calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by sex (female vs male), with weights proposed by Greenland and Robins.
Source: Table 14.2.5.1.1 with reviewer edits

Reviewer Comments: ***UUI 100% responder analyses is synonymous with complete continence (or "cure" of Wet OAB). Vibegron 75 mg showed statistically significant differences in the 100% UUI responder analyses of 6.3% - from 25.3% for vibegron vs. 19% for placebo. This difference is small.***

Urgency Episode 50% Responder Analysis

Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant difference from placebo in the percent of OAB subjects with a 50% reduction from baseline at Week 12 in urgency episodes (adjusted difference from placebo of 6.8%, p = 0.0235). Compared with tolterodine treatment, vibegron demonstrated a numerically greater proportion of subjects with a 50% reduction from baseline in the number of urgency episodes at week 12.

For placebo-adjusted tolterodine, the 50% urgency responder rate did not reach statistical significance at week 12.

The following table presents the results of all OAB subjects with at least a 50% reduction from baseline to Week 12 in daily urgency episodes where urgency is defined as checking "need to urinate immediately" on the PVD.

Table 19: 50% Urgency Responder Vibegron and Tolterodine Week 12 FAS

Statistic	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Subjects with at least 50% reduction in urgency episodes from baseline at Week 12			
Unadjusted n (%)	199 (38.3)	227 (43.2)	172 (41.2)
Adjusted n (%)	171 (32.8)	208 (39.5)	152 (36.4)
Active – Placebo[a]			
CMH Difference		6.8	3.7
95% CI		0.9 to 12.7	-2.5 to 10.0
p-value		0.0235	0.2400

Notes: MI was used to impute values missing for any reason at the weeks analyzed.
Presented frequencies and the denominator used for percentages were based on subjects in the FAS and randomized treatment.
a The difference in proportion and corresponding CI and p-value was calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by OAB type (Wet vs Dry) and sex (female vs male), with weights proposed by Greenland and Robins.
Source: Table 14.2.6.1.1 with reviewer edits

<u>Reviewer Comments:</u> vibegron 75 mg showed statistically significant differences in 50% responder endpoint for urgency/need to urinate immediately but the difference from placebo was small (7%). As noted in the section for the urgency endpoint, the DCOA team's anchor-based analyses determined that a higher threshold (60%) for the urgency responder endpoint was reflective of clinical meaningful within-patient change threshold in Study 3003. (b) (4)

Change from Baseline in Total Incontinence Episodes

At baseline, the average daily number of total incontinence episodes (inclusive of urge and stress types) was similar across the 3 treatment groups. Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant reduction from baseline at Week 12 in the adjusted average daily number of total incontinence episodes as compared with placebo treatment ($p < 0.0001$). Vibegron treatment demonstrated numerically greater decreases in the number of average daily total incontinence episodes compared with tolterodine treatment.

Placebo-adjusted total incontinence episodes decreases from baseline for tolterodine also reached statistical significance.

The following table shows daily average incontinence episodes in OAB wet patients for vibegron and tolterodine at week 12:

Table 20: Total Daily Average Incontinence Episodes Change from Baseline in OAB Wet (FAS-I) Week 12

	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319
Baseline			
N	405	403	319
Mean (SD)	4.17 (3.823)	4.14 (3.631)	4.06 (3.071)
Week 12			
n	372	383	286
Mean (SD)	2.50 (3.087)	1.89 (3.120)	1.89 (2.353)
Change from baseline at Week 12			
n	372	383	286
LS means (SE)	-1.6 (0.15)	-2.3 (0.15)	-2.0 (0.16)
95% CI	-1.9 to -1.3	-2.6 to -2.0	-2.4 to -1.7
Active – Placebo			
LS means difference (SE)		-0.7 (0.16)	-0.5 (0.17)
95% CI		-1.0 to -0.4	-0.8 to -0.1
P-value		< 0.0001	0.0074

Notes: Covariates included in the mixed model for repeated measures were study visit, sex, region, baseline number of incontinence episodes, and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
Source: Table 14.2.7.1.2 with reviewer edits

<u>Reviewer Comments:</u> This endpoint also met statistically significance for vibegron over placebo, but the mean difference between vibegron and placebo was small (-0.7 episodes per day).

Change from Baseline in Coping Score from OAB-q LF

(b) (4)

(b) (4)

The following table presents the results of the key secondary endpoint of change from baseline at Week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (1-week recall) in all OAB subjects (with missing item imputation).

Table 21: Coping Score from OAB-q LF Change from Baseline Week 12 with Missing Item Imputation

(b) (4)

The DCOA team was also consulted to determine content validity and other measurement properties of the OAB-LF Coping domain, as well as the Sponsor's proposed thresholds for meaningful within-patient score change for this measure. The DCOA team had the following conclusions on the OAB-q LF Coping domain:

- (There is) inadequate documentation of content validity to support the OAB-q LF Coping domain (b) (4)

(b) (4)

Reviewer Comments: ***Thus, the DCOA consult team concluded that there is inadequate documentation to support the OAB-q LF coping domain*** (b) (4)

Change from Baseline in Voided Volume Per Micturition

At baseline, the average volume voided per micturition was similar across the 3 treatment groups. Vibegron treatment resulted in a statistically significant increase in adjusted-average micturition voided volume from baseline, compared with placebo treatment at week 12 ($p < 0.0001$). Vibegron demonstrated numerically greater increases in average volume voided per micturition compared with tolterodine treatment.

In the comparison between placebo and tolterodine, the Week 12 increase from baseline in the adjusted average volume voided per micturition reached statistical significance.

The following table presents the average micturition voided volume change from baseline in all patients at week 12.

Table 22: Average Micturition Voided Volume Change from Baseline Week 12 (FAS)

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Baseline			
n	514	524	415
Mean (SD)	148.3 (60.67)	155.4 (63.07)	147.0 (60.79)
Week 12			
n	478	490	375
Mean (SD)	149.1 (69.42)	175.3 (81.78)	162.1 (72.96)
Change from Baseline at Week 12			
n	478	490	375
LS means (SE)	2.2 (3.28)	23.5 (3.26)	15.5 (3.52)
95% CI	-4.2 to 8.7	17.1 to 29.9	8.6 to 22.4
Active – Placebo			
LS means difference (SE)		21.2 (3.52)	13.3 (3.76)
95% CI		14.3 to 28.1	5.9 to 20.7
P-value		< 0.0001	< 0.001

Notes: Covariates included in the mixed model for repeated measures were study visit, OAB type, sex, region, baseline volume (mL) and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
Source: Table 14.2.9.1.2 with reviewer edits

<u>Reviewer Comments:</u> This endpoint also met statistical significance when comparing vibegron to placebo but clinical meaningfulness is uncertain as the mean difference between groups for change from baseline in average voided volume is small (21 mL).

Additional Secondary Efficacy Endpoints:
<u>Reviewer Comments:</u> The Sponsor is not seeking labeling claims for the following secondary endpoints.

The following are additional secondary efficacy endpoints, listed in order

Change from Baseline in Total HRQL Score from the OAB-q LF
At baseline, the mean OAB-q LF Total HRQL Score was similar across the 3 treatment groups. Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant increase from baseline at Week 12 in the adjusted mean OAB-q LF Total HRQL Score as compared with placebo treatment ($p < 0.001$). Vibegron treatment demonstrated numerically greater increases in the OAB-q LF Total HRQL Score compared with tolterodine treatment.

In the comparison between placebo and tolterodine, the Week 12 increase from baseline in the adjusted mean OAB-q LF Total HRQL Score reached statistical significance.

The following table summarizes total HRQL Score from OAB-q LF (1-week recall) in all patients with missing item imputation.

Table 23: Total HRQL Score from the OAB-q LF Change from Baseline Week 12 with Missing Item Imputation

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Baseline			
n	518	524	416
Mean (SD)	63.74 (23.473)	62.71 (24.916)	64.53 (22.902)
Week 12			
n	504	512	400
Mean (SD)	76.62 (21.068)	80.11 (20.180)	80.05 (19.891)
Change from Baseline at Week 12			
n	504	512	400
LS means (SE)	10.8 (1.13)	14.6 (1.12)	13.7 (1.19)
Active – Placebo			
LS means difference (SE)		3.8 (1.06)	2.9 (1.13)
P-value		< 0.001	0.0114

Notes: Higher scores correspond to a higher quality of life.
Covariates included in the mixed model for repeated measures were study visit, sex, region, OAB type, baseline score, and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
If < 50% of items were available, the subscore was regarded as missing; however, if 2' 50% of items were available, the subscore included missing items imputed as the average of the remaining non-missing items for subscore.
Source: Table 14.2.8.1.4 with reviewer edits

Change from Baseline in Symptom Bother Score from the OAB-q LF

At baseline, the mean OAB-q LF Symptom Bother Score was similar across the 3 treatment groups. Vibegron treatment resulted in a statistically significant decrease from baseline at Week 12 in the adjusted mean OAB-q LF Symptom Bother Score as compared with placebo treatment ($p < 0.0001$). Vibegron demonstrated numerically greater decreases in the OAB-q LF Symptom Bother Score compared with tolterodine treatment.

In the comparison between placebo and tolterodine, the Week 12 decrease from baseline in the adjusted mean OAB-q LF Symptom Bother reached statistical significance.

The following table summarizes results from Symptom Bother Score from the OAB-q LF (1-week recall) in all patients with missing item imputation.

Table 24: Symptom Bother Score from OAB-q LF Change from Baseline with Missing Item Imputation Week 12 (FAS)

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Baseline			
N	518	524	416
Mean (SD)	50.07 (20.642)	49.68 (21.961)	48.01 (20.611)
Change from Baseline at Week 12			
N	504	512	400
LS means (SE)	-12.8 (1.25)	-19.6 (1.24)	-17.4 (1.31)
Active – Placebo			
LS means difference (SE)		-6.9 (1.17)	-4.6 (1.25)
P-value		< 0.0001	< 0.001

Notes: Lower scores correspond to a higher quality of life.
Covariates included in the mixed model for repeated measures were study visit, sex, region, OAB type, baseline score, and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
If < 50% of items were available, the subscore was regarded as missing; however, if 2' 50% of items were available, the subscore included missing items imputed as the average of the remaining non-missing items for subscore.
Source: Table 14.2.8.1.4 with reviewer edits

Percent of Subjects with < 8 Average Daily Micturitions

At Week 12 and all other timepoints (Weeks 2, 4, and 8), the adjusted number of subjects with < 8 average daily micturitions was statistically significantly greater for subjects who received vibegron compared with subjects who received placebo ($p \leq 0.0074$). Vibegron treatment demonstrated numerically greater numbers of subjects with < 8 average daily micturitions compared with tolterodine treatment at all timepoints.

Total Incontinence Episodes 50% Responder Analysis

At Week 12 and all other timepoints (Weeks 2, 4, and 8), the adjusted number of subjects with at least a 50% reduction from baseline in total incontinence episodes was statistically significantly greater for subjects who received vibegron compared with subjects who received placebo ($p < 0.001$).

Change from Baseline in Overall Bladder Symptoms from the PGI-Severity Scale
At baseline, the mean PGI-Severity Score was similar across the 3 treatment groups. Vibegron treatment 75 mg resulted in a statistically significant decrease from baseline at Week 12 in the adjusted mean PGI-Severity Score as compared with placebo treatment ($p < 0.0001$).

The following table summarizes findings from the Patient Global Impression of Severity (PGI-Severity) in all patients.

Table 25: Patient Global Impression-Severity Score Change from Baseline Week 12-FAS

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Baseline			
n	519	525	417
Mean (SD) severity score	3.03 (0.645)	3.02 (0.619)	2.99 (0.639)
Change from Baseline at Week 12			
n	484	494	382
LS Means (SE)	-0.5 (0.04)	-0.8 (0.04)	-0.7 (0.04)
Active – Placebo			
LS Means Difference (SE)		-0.2 (0.04)	-0.1 (0.05)
P-Value		< 0.0001	0.0055

Notes: Subjects responded to the question "Over the past week, how would you rate your overactive bladder symptoms?" with one of the following possible responses (response value): None (1), Mild (2), Moderate (3), or Severe (4).
Lower scores correspond to a higher quality of life.
Covariates included in the mixed model for repeated measures were study visit, OAB type, sex, region, baseline score, and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
Source: Table 14.2.12.1.2 with reviewer edits

At baseline, there was no difference across the 3 treatment groups in the proportion of subjects providing the most favorable response (ie, a response of "None") to the PGI-Severity question. At the end of treatment assessment, approximately twice as many subjects in the vibegron group compared with the placebo group had provided the most favorable response to the PGI-Severity question. The following table summarizes the most favorable response in the PGI-Severity question at baseline and end of treatment 12 weeks in all patients.

Table 26: Most Favorable Response in the Patient Global Impression-Severity Question at Baseline and End of Treatment-FAS

	Placebo N = 520 n (%)	Vibegron 75 mg N = 526 n (%)	Tolterodine ER 4 mg N = 417 n (%)

Subjects with a response of "None" when asked "Over the past week, how would you rate your overactive bladder symptoms?"[a]			
Baseline	4 (0.8)	4 (0.8)	3 (0.7)
End of Treatment	31 (6.0)	62 (11.8)	32 (7.7)

[a] Possible responses were None, Mild, Moderate, or Severe
Source: Table 14.2.12.1.1 with reviewer edits

Overall Control Over Bladder Symptoms from the PGI-Control Score (Change from Baseline)
At baseline, the mean PGI-Control Score was similar across the 3 treatment groups. Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant decrease from baseline at Week 12 in the adjusted mean PGI-Control Score as compared with placebo treatment ($p < 0.0001$).

The following table summarizes overall control over bladder symptoms based on the PGI-Control in all patients at week 12.

Table 27: PGI-Control Score Change from Baseline Week 12 FAS

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Baseline			
n	519	525	417
Mean (SD)	3.16 (0.964)	3.23 (0.911)	3.17 (0.934)
Change from Baseline at Week 12			
n	484	494	382
LS Means (SE)	-0.7 (0.05)	-1.0 (0.05)	-0.9 (0.05)
Active – Placebo			
LS Means Difference (SE)		-0.3 (0.05)	-0.2 (0.06)
P-Value		< 0.0001	< 0.001

Notes: Subjects responded to the question "Over the past week, how much control did you have over your overactive bladder symptoms?" with one of the following possible responses (response value): Complete control (1), A lot of control (2), Some control (3), Only a little control (4), or No control (5).
Lower scores correspond to a higher quality of life.
Covariates included in the mixed model for repeated measures were study visit, OAB type, sex, region, baseline score, and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.
Source: Table 14.2.12.1.2 with reviewer edits

The proportion of subjects providing the most favorable response (ie, a response of "Complete control") to the PGI-Control question was slightly higher in the placebo and tolterodine groups compared with the vibegron group at baseline. By the end of treatment, the proportion of subjects in the vibegron group that had provided the most favorable response to the PGI-

Control question was higher that of the placebo group. The following table summarizes the proportion of all patients with complete control at baseline and end of treatment at week 12.

Table 28: Complete Control Response for PGI-Control Question Baseline and End of Treatment Week 12 (FAS)

	Placebo N = 520 n (%)	Vibegron 75 mg N = 526 n (%)	Tolterodine ER 4 mg N = 417 n (%)
Subjects with a response of "Complete control" when asked "Over the past week, how much control did you have over your overactive bladder symptoms?"[a]			
Baseline	30 (5.8)	20 (3.8)	21 (5.0)
End of Treatment	50 (9.6)	92 (17.5)	62 (14.9)

[a] Possible responses were Complete control, A lot of control, Some control, Only a little control, or No control.
Source: Table 14.2.12.1.1 with reviewer edits

Dose/Dose Response

The Sponsor studied one dose, 75mg daily oral dose, in this phase 3 study which has not been studied previously during drug development. Results from previous Phase 2 studies, conducted at doses of 3 mg, 15mg, 50 mg and 100 mg daily led to the decision to pursue the single 75 mg daily dose in study 3003.

Durability of Response

Study 3003 was a 12-week study, followed by the randomized, double-blind, active-controlled, extension Study 3004 that evaluated durability of effects. See section 6.2 for a discussion of the results from Study 3004.

Persistence of Effect

See Section 6.2 for a discussion of results from Study 3004, the randomized, double-blind, active-controlled extension study to study 3003.

Additional Analyses Conducted on the Individual Trial

Not Applicable

6.2. RVT-901-3004: An International Phase 3, Randomized, Double-Blind, Active (Tolterodine)-Controlled Multicenter Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder

6.2.1. Study Design

Overview and Objective

Study 3004: A Phase 3, Randomized, Double-Blind, Active-Controlled Extension Study

Title: An International, Phase 3, Randomized, Double-Blind, Active (Tolterodine)-Controlled, Multicenter, Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder

Purpose and Objectives:

- Primary: To evaluate the safety and tolerability of vibegron for up to 52 weeks in subjects with symptoms of OAB who previously completed treatment in 3003
- Secondary Efficacy**:** To evaluate the efficacy of vibegron in subjects with symptoms of OAB
- Secondary Other: To evaluate the effect of vibegron on subject-perceived outcomes in subjects with symptoms of OAB

Trial Design

Design: Study 3004 was a Phase 3, double-blind, active (tolterodine)-controlled, parallel-group, multicenter, 40-week extension study to Study 3003 designed to evaluate the safety, tolerability, and efficacy of vibegron 75 mg in men and women with symptoms of OAB who completed participation in Study 3003 (with planned enrollment capped at 500 subjects). The study consisted of a randomized, double-blind, Treatment Period (40 weeks) and a Safety Follow-up Period (4 weeks). Subjects randomized in Study 3003 to either the vibegron or the tolterodine ER group continued their same treatment once daily in a blinded fashion for an additional 40 weeks during this extension study; subjects 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 for 40 weeks during the extension study 3004.

Study Endpoints

Primary study endpoint:

- Incidence of treatment-emergent AEs by system organ class (SOC) and preferred term (PT)

Secondary efficacy endpoints included the following:

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

Exploratory efficacy endpoints included the following:

- Percent of all OAB subjects with at least a 50% reduction from baseline in urgency episodes per 24 hours at Week 52
- Percent of OAB Wet subjects with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 52
- Percent of OAB Wet subjects with 100% reduction from baseline CFB at Week 52 in average volume voided per micturition in all OAB subjects
- Percent of OAB subjects with at least a 50% reduction from baseline in total urinary incontinence per 24 hours at Week 52

Statistical Analysis Plan

Efficacy analyses were for descriptive purposes only and were conducted using the FAS-Extension (FAS-Ext) population. The key statistical principles employed for efficacy evaluations in Study 3003, including use of the MMRM with restricted maximum likelihood estimation, were also used for Study 3004. The Kenward-Roger adjustment was used with restricted (or residual) maximum likelihood (REML) to make statistical inference. Adjusted means for each treatment group and visit were estimated along with 95% confidence intervals. No formal statistical comparisons were made. Only the 52-week cohort (those on active treatment in both Studies 3003 and 3004) were included in the model.

Multiple imputation methods were used to estimate missing values for the exploratory responder endpoints and to estimate the percent of responders and associated 95% confidence intervals for each treatment and visit. Large sample theory (normal approximation to the binomial) was used to determine the 95% confidence intervals.

A separate FAS definition (FAS-Ext-I) with an additional criterion was used to define the analysis population for incontinence endpoints, since incontinence endpoints only applied to subjects meeting the definition of OAB Wet.

Protocol Amendments

There were 2 major protocol amendments for Study 3004 that were in line with Study 3003's

protocol amendments. The following table summarizes the major changes which included the following two notable changes: 1) moving a set of secondary endpoints to exploratory endpoints in Version 3.0 and 2) change of responder analysis percentage reduction from 70% to 75% in Version 2.0.

Table 29: Summary of Study 3004 Protocol Major Changes

Version	Location of Change Section in Protocol	Description of Change
3.0	1	The approximate number of study sites was updated.
3.0	1; 3; 9.3.1	The following endpoints previously included as "Secondary Efficacy" endpoints were moved to "Exploratory" endpoints. • Percent of all OAB patients with a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 52; • Percent of OAB Wet patients with a 75% reduction from baseline in UUI episodes per 24 hours at Week 52; • CFB at Week 52 in average volume voided per micturition in all OAB patients; • CFB at Week 52 in Coping Score from the OAB-q LF (1-week recall) in all OAB patients; • CFB at Week 52 in Health-related Quality of Life (HRQL) Total Score from the OAB-q LF (1-week recall) in all OAB patients; • CFB at Week 52 in Symptom Bother Score from the OAB-q-LF (1-week recall) in all OAB patients.
2.0	1; 3; 9.3.1	Addition of two exploratory efficacy endpoints (CFB at Week 52 in average number of nighttime voids for all patients; CFB at Week 52 in average number of nighttime voids for patients with nocturia at baseline).
2.0	1; 3; 9.2.2; 9.3.1; 9.5.1	Statistical Methods: Change of 5% in response efficacy endpoints (70% to 75%); change in statistical analysis from LOCF to multiple imputation; subgroup analyses changed to include primary MMRM analysis model with a subgroup by treatment interaction term.
1.1	8.6	Added adverse events suggestive of cystitis or urinary tract infection and moved liver test values to end of list.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Sponsor stated that all clinical studies supporting the safety and efficacy of vibegron in this application (NDA 213006) were designed and conducted in accordance with Good Clinical Practice, including review and approval by an independent ethics committee and informed consent for subjects, and ethical principles defined in the Declaration of Helsinki (World Health Organization). This statement applies to the studies conducted as IND studies under IND 106410 and to studies (and sites) not conducted under the IND.

Financial Disclosure

The Sponsor included a financial disclosure and no concerns were raised for this study as no investigator had a financial disclosure.

Patient Disposition

Study Population: Of the 506 subjects randomized in the study, 505 received at least 1 dose of double-blind study drug in the Treatment Period (273 vibegron; 232 tolterodine ER) and 485 (266 vibegron; 219 tolterodine ER) also had at least 1 subsequent evaluable change from baseline micturition measurement in the extension study 3004 comprising the FAS-Ext population set used for efficacy evaluations. A separate FAS definition (FAS-Ext-I) with an additional criterion was used to define the analysis population for incontinence endpoints, since incontinence endpoints only applied to subjects meeting the definition of OAB Wet (212 vibegron; 170 tolterodine ER). The study had a high completion rate, with 430 of 506 subjects (85.0%) completing the study. Of the 76 subjects who discontinued from the study prior to Week 52, most withdrew consent (32 [42.1%], were lost to follow up (15 [19.7%]) or had an AE that led to withdrawal (12 subjects [15.8%]).

Protocol Violations/Deviation

Using prespecified criteria, each deviation in the master protocol deviation list was assigned a classification by the Urovant clinical team, which was reviewed by the (b) (4) and the Urovant study team for final review and approval of the classification. Each protocol deviation was classified as either "major" or "minor". A major protocol deviation was one that may have had an impact on subject safety, substantially alter risks to subjects, affect the integrity of study data, or influence the conduct of the study. Major protocol deviations were further classified as follows: Major (Safety), Major (Efficacy), Major (Safety and Efficacy), Major (Other), or Major (Efficacy, Duplicate Patient). A minor protocol deviation was one that did not

impact subject safety, substantially alter risks to subjects, nor compromise the integrity of the study data, notably the outcome variables.

Subjects with major efficacy-related and compliance-related protocol deviations were excluded from the PPS-Ext and the PPS-Ext-I under the assumption that the deviation may have an impact on the efficacy analysis. After unblinding the study, it was discovered that the criterion for excluding subjects from the per-protocol populations due to undercompliance was applied incorrectly at the blinded-data review meeting. The criterion, as pre-specified in the protocol deviation plan, was to exclude subjects with < 75% compliance between Visit 10 and Visit 11.

However, at the blinded-data review meeting, this rule was incorrectly applied based on overall compliance. Since this was a pre-specified rule that could be objectively applied, the study team decided to correct this error and update the per-protocol populations, even though the study was unblinded at the time.

The Sponsor reported that the majority of protocol deviations were minor and did not affect the study conduct or interpretation of the study results. Overall, major protocol deviations were reported for 13.2% of subjects, and 5.6% and 0.2% of subjects had a major efficacy-related or efficacy and safety- related protocol deviation in the following table, which excluded the patients from the PPS-Ext and PPS-Ext-I.

Table 30: Major Protocol Deviation Summary Study 3004- FAS Ext

Protocol Deviation	40-weeks Vibegron 75mg (N=90)	52-weeks Vibegron 75mg (N=176	Overall Vibegron 75mg (N=266) n (%)	40-weeks Tolterodine ER 4mg (N=83) n (%)	52-weeks Tolterodine ER 4mg (N=136) n (%)	Overall Tolterodine ER 4mg (N=219) n (%)	Overall (N=485) n (%)
Subjects with at Least One Major Protocol Deviation	8 (8.9)	27 (15.3)	35 (13.2)	8 (9.6)	21 (15.4)	29 (13.2)	64 (13.2)
Subjects with Major Protocol Deviation by Classification							
Efficacy	2 (2.2)	11 (6.3)	13 (4.9)	5 (6.0)	9 (6.6)	14 (6.4)	27 (5.6)
Efficacy and Safety	0	1 (0.6)	1 (0.4)	0	0	0	1 (0.2)
Safety	6 (6.7)	17 (9.7)	23 (8.6)	3 (3.6)	16 (11.8)	19 (8.7)	42 (8.7)
Other	0	1 (0.6)	1 (0.4)	0	2 (1.5)	2 (0.9)	3 (0.6)
Subjects with Any Major Protocol Deviation by Category							
Inclusion Criteria	0	2 (1.1)	2 (0.8)	1 (1.2)	1 (0.7)	2 (0.9)	4 (0.8)
Exclusion Criteria	2 (2.2)	6 (3.4)	8 (3.0)	0	6 (4.4)	6 (2.7)	14 (2.9)
ICF	0	0	0	0	1 (0.7)	1 (0.5)	1 (0.2)
Missed Study Visit	1 (1.1)	3 (1.7)	4 (1.5)	1 (1.2)	2 (1.5)	3 (1.4)	7 (1.4)

Procedure Not Per	3 (3.3)	15 (8.5)	18 (6.8)	6 (7.2)	10 (7.4)	16 (7.3)	34 (7.0)
Concomitant	0	0	0	1 (1.2)	0	1 (0.5)	1 (0.2)
Lab Sample	1 (1.1)	0	1 (0.4)	0	1 (0.7)	1 (0.5)	2 (0.4)
Other	1 (1.1)	2 (1.1)	3 (1.1)	0	4 (2.9)	4 (1.8)	7 (1.4)
Subjects with at Least One Major Efficacy-Related Protocol Deviation	2 (2.2)	11 (6.3)	13 (4.9)	5 (6.0)	9 (6.6)	14(6.4)	27 (5.6)
Inclusion Criteria	0	1 (0.6)	1 (0.4)	1 (1.2)	1 (0.7)	2 (0.9)	3 (0.6)
Exclusion Criteria	1 (1.1)	4 (2.3)	5 (1.9)	0	2 (1.5)	2 (0.9)	7 (1.4)
Not Per Protocol	0	5 (2.8)	5 (1.9)	4 (4.8)	3 (2.2)	7 (3.2)	12 (2.5)
Concomitant Medication	0	0	0	1 (1.2)	0	1 (0.5)	1 (0.2)
Other	1 (1.1)	2 (1.1)	3 (1.1)	0	4 (2.9)	4 (1.8)	7 (1.4)

Notes: Presented frequencies and the denominator used for percentages are based on subjects in the FAS-Ext and the treatment randomized.
Only major efficacy- and compliance-related protocol deviations excluded a subject from the PP-Ext and PP-Ext-I populations. Efficacy-related included the classifications of "Efficacy", "Efficacy Duplicate Patient", and "Efficacy and Safety".
A subject may have been included in more than one category of major protocol deviation.
Source: Table 14.1.2.1 with reviewer edits

Demographic Characteristics

Subject characteristics in Study 3004 were consistent with those of Study 3003 and were balanced between treatment groups. Among the FAS-Ext population, 382 (78.8%) were in the OAB Wet stratum and 103 (21.2%) were in the OAB Dry stratum. The study population was predominantly female (78.1%). The mean age was 61.2 years. Most subjects were white (76.7%) or black/African American (14.4%). Across treatment groups, the mean numbers of average daily micturitions, UUI episodes, and urgency episodes at baseline were 11.32, 2.34, and 7.87, respectively. The treatment groups were well balanced with respect to age, gender, race, OAB type (Wet vs Dry), and prior use of anticholinergics or β3-AR agonists.

Reviewer Comments: The subject characteristics and demographics in Study 3004 were consistent with those in Study 3003 with similar distribution at baseline - with the exception that the proportion of women dropped from 85% in Study 3003 to 78% in Study 3004 with concurrent rise of the proportion of men from 15% in Study 3003 to 22% in Study 3004.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
See section below on concomitant medications.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Prior OAB Medications
In the overall study population and in the overall vibegron and overall tolterodine groups, approximately 20% of subjects had received at least 1 prior OAB medication. There was a slight imbalance within the tolterodine group, with a higher proportion of subjects in the 40-weeks group (26.4%) compared with the 52-weeks group (17.0%) having received at least 1 prior OAB medication.

Treatment Compliance
Overall, high rates of compliance were observed; categorical assessments (< 75%, ≥ 75% to ≤ 125%, or > 125%) demonstrated that ≤ 2.2% of subjects were included in < 75% compliance category across all vibegron and tolterodine treatment groups (SAF-Ext and FAS-Ext) - for both tablets and capsules - during the Double-blind Period.

Efficacy Results – Endpoints

Efficacy Results-Secondary Efficacy Endpoints
As safety is the primary endpoint for Study 3004, extension study, the secondary endpoints are the efficacy endpoints, consistent with the co-primary endpoints of Study 3003, micturitions and UUI episodes.

For the efficacy endpoint results, the description focuses on the cohorts of patients who received study drug (vibegron or tolterodine ER) for 52 weeks. Results for patients who received placebo in Study 3003 and switched to active study drug at the start of Study 3004 with 40 weeks of vibegron treatment are not included in the main efficacy analysis for Study 3004 as these patients did not receive the full 52 weeks of treatment.

Micturition Efficacy Endpoint:
The Sponsor reports that the results of Study 3004 (the extension study) show that the reductions in the average daily number of micturitions were maintained over 52 weeks of vibegron treatment (LS means difference [standard error {SE}] for CFB at Week 52: -2.4 [0.24], 95% CI: -2.9, -2.0). Larger reductions were shown for vibegron relative to tolterodine treatment for the same time period. The following table summarizes the micturition count changes from baseline in Study 3004 at Week 52.

Table 31: Study 3004 Micturitions Average Daily Number Change from Baseline Week 52 (MMRM) in FAS-Ext

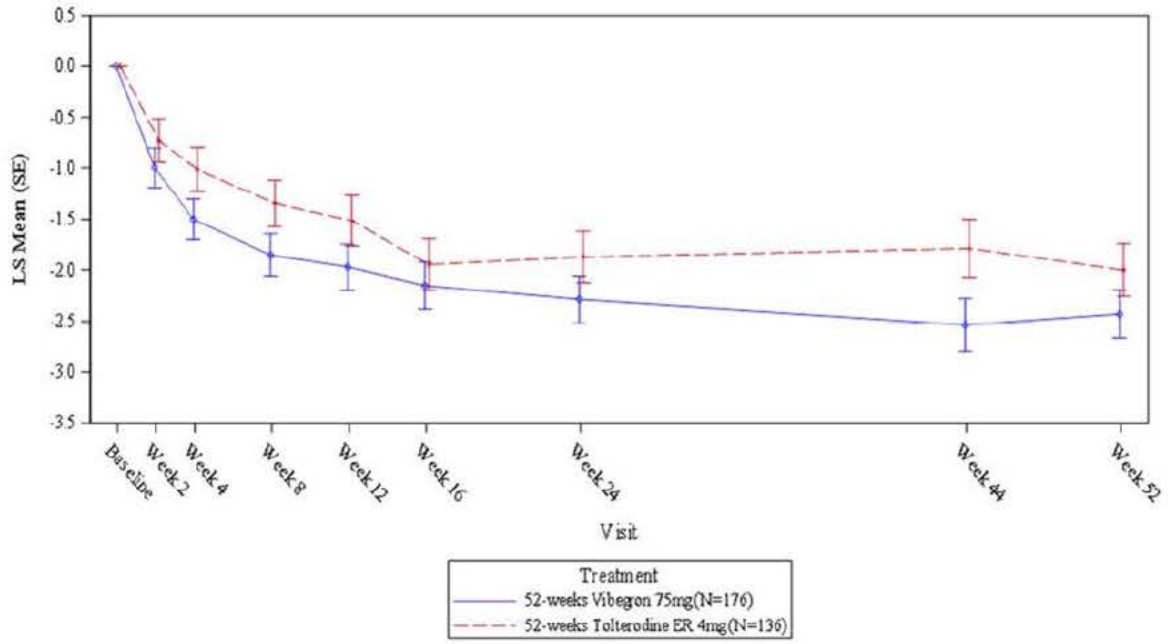
	Vibegron 75mg N = 176	Tolterodine ER 4mg N = 136
Baseline Average Daily Number of Micturitions		
n	176	136

Mean (SD)	11.32 (3.415)	11.33 (3.218)
Change from Baseline at Week 52 in Average Daily Number of Micturitions		
n	152	120
LS Means (SE)	-2.4 (0.24)	-2.0 (0.26)
95% CI	-2.9, -2.0	-2.5, -1.5

CI = confidence interval; LS = least squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error
Notes: Baseline value based on run-in diaries from Study 3003.
Covariates included in the mixed model for repeated measures were study visit, treatment, treatment by study visit interaction, baseline and the statistically significant terms in Study 3003: OAB type and sex.
Source: Study 3004 CSR, Table 14.2.1.2 with reviewer edits

The following figure shows the average daily micturitions from baseline in Study 3004 for the FAS-Extension patients.

Figure 7: Study 3004 Micturitions Average Daily Number Plot of LS Means (SE) Change from Baseline FAS-Ext



Notes: Baseline value based on run-in diaries from Study 3003.
LS means (SE) were computed from the MMRM model displayed in Table 14.2.1.2 for 52-week groups only
Source: Study 3004 CSR, Figure 14.2.1.5

UUI Episodes Efficacy Endpoint:
The Sponsor reports that results of Study 3004 (the extension study) show that durable reductions in the average daily number of UUI episodes were maintained over 52 weeks of vibegron treatment (LS means difference [SE] for CFB at Week 52: -2.2 [0.15], 95% CI: -2.5, -

1.9). Greater reductions were consistently observed for the vibegron group compared with the tolterodine group at all timepoints through 52 weeks of treatment (LS means difference [SE] for CFB at Week 52 for tolterodine ER: -1.7 [0.17]; 95% CI: -2.0, -1.3).

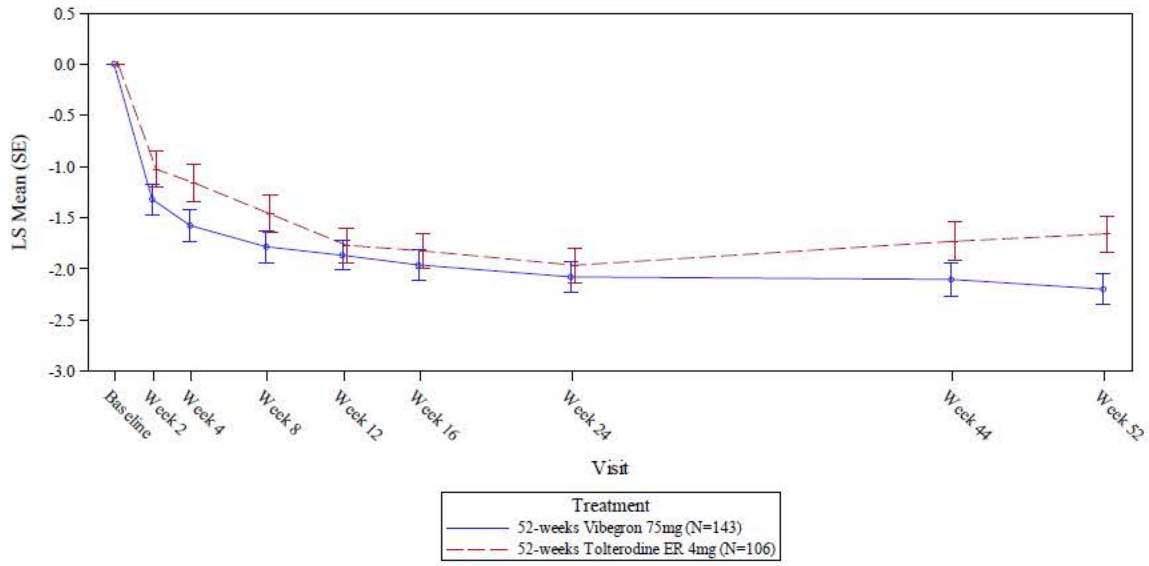
Table 32: Study 3004 UUI Average Daily Number Change from Baseline Week 52 FAS-Ext-I

	Vibegron 75mg (N=143)	Tolterodine ER 4mg (N=106)
Baseline Average Daily Number of UUI Episodes		
Baseline		
n	143	106
Mean (SD)[a]	3.18 (2.837)	3.00 (2.038)
Change from Baseline at Week 52 in Average Daily Number of UUI Episodes		
n	125	91
LS Means (SE)[b]	-2.2 (0.15)	-1.7 (0.17)
95% CI	-2.5, -1.9	-2.0, -1.3

CI = confidence interval; LS = least squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error; UUI = urge urinary incontinence
Notes: A UUI episode is defined as having "urge" as the main reason for the leakage as indicated on the voiding diary, regardless of whether more than one reason for leakage is checked. Average daily number of UUI episodes was calculated as the total number of UUI that occurred on a complete diary day divided by the number of complete diary days in a voiding diary. If <4 complete diary days were available, then the endpoint was considered missing.
Baseline value based on run-in diaries from Study 3003. Weeks are relative to start of double-blind treatment in Study 3003.
[a] Descriptive statistics
[b] Mixed model for repeated measures; the covariates included in the MMRM were study visit, treatment, treatment by study visit interaction, baseline and the statistically significant terms in Study 3003: OAB type and sex. Per protocol, only subjects on active treatment in both Study 3003 and Study 3004 were included in the model.
Source: Study 3004 CSR, Tables 14.2.2.2, 14.2.4.1, and 14.2.4.2 with reviewer edits

The following figure shows the average daily number of UUI episodes in the FAS Extension Incontinent population from baseline in Study 3004.

Figure 8: Study 3004: UUI Episodes Average Daily Number Change from Baseline LS Means (SE) (MMRM) FAS-Ext I



Note: Baseline value based on run-in diaries from Study 3003.
LS means (SE) were computed from the MMRM model displayed in Table 14.2.2.2 for 52-week groups only.
Source: Figure 14.2.2.5

Urgency Efficacy Endpoint:

For subjects treated with vibegron 75 mg, the reduction from baseline in average daily number of urgency episodes had a rapid onset (within 2 weeks, as demonstrated by assessments conducted under the Study 3003 protocol), and the decrease was maintained over 52 weeks.

Greater reductions were observed for the vibegron group compared with the tolterodine group at all timepoints.

The following table summarizes urgency episodes at week 52 compared to baseline values in the FAS-Ext patient population.

Table 33: Study 3004: Urgency Average Daily Urgency Episodes Change from Baseline Week 52 (MMRM) FAS-Ext

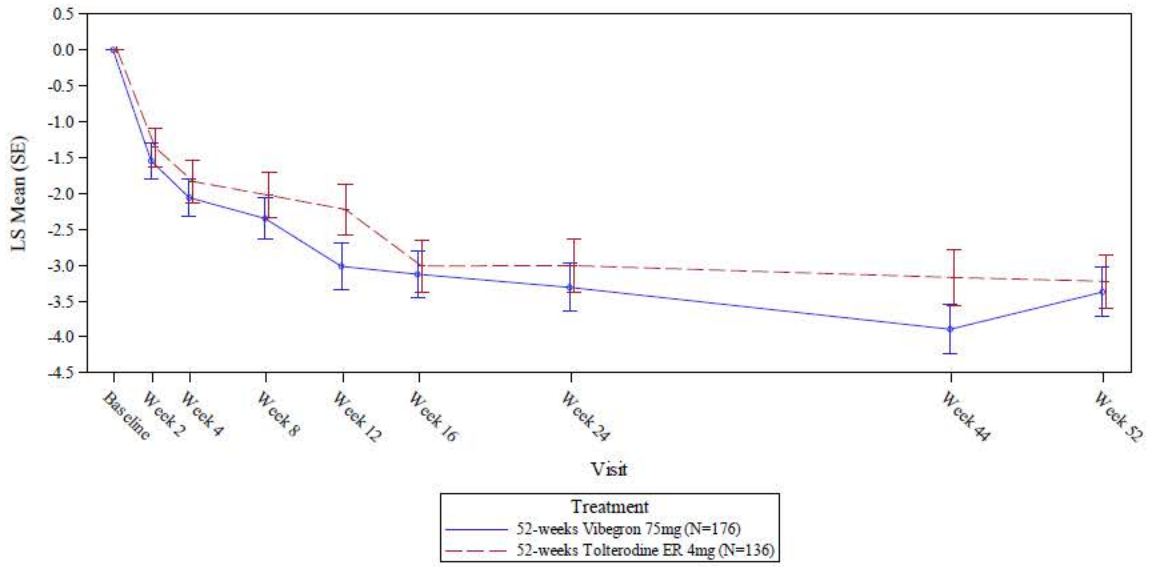
	Vibegron 75mg (N=176)	Tolterodine ER 4mg (N=136)
Baseline Average Daily Number of Urgency Episodes		
n	176	136

Mean (SD)[a]	8.0 (4.59)	8.0 (3.71)
Change from Baseline at Week 52 in Average Daily Number of Urgency Episodes		
n	152	120
LS Means (SE)[b]	-3.4 (0.34)	-3.2 (0.37)
95% CI[b]	-4.0, -2.7	-4.0, -2.5

CI = confidence interval; LS = least squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error; UUI = urge urinary incontinence
Notes: Baseline value based on run-in diaries from Study 3003.
Covariates included in the mixed model for repeated measures were study visit, treatment, treatment by study visit interaction, baseline and the statistically significant terms in Study 3003: OAB type and sex.
Source: Study 3004 CSR Table 14.2.3.1, Table 14.2.3.2 with reviewer edits

The following figure plots the average daily number of urgency episodes and change from baseline in the FAS-Ext patient population.

Figure 9: Urgency Episodes LS Means (SE) Change from Baseline (MMRM) to Week 52 FAS-Ext



Baseline value based on run-in diaries from Study 3003.
LS means (SE) were computed from the MMRM model displayed in Table 14.2.3.2 for 52-week groups only
Source: Study 3004 CSR, Figure 14.2.3.5

Data Quality and Integrity

OSI investigated 2 of 3 requested sites for Study 3004 and deemed the inspections as NAI. See Data Quality and Integrity under section 6.1.2 for Study 3003.

Efficacy Results – Secondary and other relevant endpoints

Additional Predefined Efficacy Endpoints:
Vibegron maintained changes in OAB symptoms through Week 52 across all additional key efficacy endpoints, including the CFB in the OAB-q LF Coping Score and the average voided volume per micturition as shown in the table below. Vibegron demonstrated numerically greater improvements in these endpoints compared with 52 weeks of tolterodine treatment.

Table 34: Study 3004: Summary Key Efficacy Endpoints Change from Baseline Week 52 FAS-Ext

	Vibegron 75mg	Tolterodine ER 4mg
Baseline Average Voided Volume per Micturition (mL) [a, b]		
n	171	130
Mean (SD)[b]	160.1 (61.98)	146.0 (57.47)
Change from Baseline Average Voided Volume per Micturition (mL) at Week 52 [a, b]		
n	145	114
Mean (SD)	25.5 (78.62)	8.8 (58.68)
Baseline OAB-q LF Coping Score a, c		
n	174	136
Mean (SD)[b]	56.4 (30.86)	59.7 (27.41)
Change from Baseline OAB-q LF Coping Score at Week 52 [a, c]		
n	164	134
Mean (SD)	27.1 (26.56)	22.1 (28.24)

LS = least squares; MMRM = mixed model for repeated measures; OAB-q LF = Overactive Bladder Questionnaire long form; SD = standard deviation; SE = standard error
Notes: Number of total incontinence episodes is defined as the number of times a subject had checked accidental leakage, and/or any reason for accidental leakage in the voiding diary.
Baseline value based on run-in diaries from Study 3003. Change from baseline was calculated by Visit Value - Baseline Value.
Weeks are relative to start of double-blind treatment in Study 3003.
For FAS-Ext, vibegron N=176, tolterodine N=136
[a] Descriptive statistics only
[b] The covariates included in the MMRM were study visit, treatment, treatment by study visit interaction, baseline and the statistically significant terms in Study 3003: OAB type and sex.
[c] The average volume voided at a visit was the arithmetic mean of all voids for which a subject had recorded the volume. For exploratory endpoints of volume voided and OAB-q LF Coping Score, Week 52 CFB statistic is mean (SD); LS means not assessed.
Source: Study 3004 CSR Table 14.2.7.1 and Table 14.2.8.1 with reviewer edits

The following table presents the results of efficacy endpoints related to predefined responder analyses, indicating reductions at Week 52 in average daily number of UUI episodes of ≥ 75% or 100% relative to baseline or a reduction in average daily number of urgency episodes of ≥ 50%.

Table 35: Study 3004- Key Responder Analyses (MI) Week 52 FAS-Ext and FAS-Ext-I

	Vibegron 75mg	Tolterodine ER 4mg
Subjects with at least 75% Reduction in UUI from Baseline at Week 52 [a]		
N[a]	143	106
Proportion	61.0	54.4
95% CI	52.6, 69.4	44.5, 64.3
Subjects with 100% Reduction in UUI from Baseline at Week 52 [a]		
N[a]	143	106
Proportion	40.8	34.2
95% CI	32.4, 49.2	24.7, 43.8
Subjects with at least 50% Reduction in Urgency Episodes from Baseline at Week 52		
N	176	136
Proportion	49.4	51.0
95% CI	41.8, 57.0	42.2, 59.9
Subjects with at least 50% Reduction in Total Incontinence at Week 52 [a]		
N	143	106
Proportion	71.1	61.9
95% CI	63.3, 78.9	52.3, 71.6

CI = confidence interval; MI = multiple imputation; UUI = urge urinary incontinence; Notes: Multiple imputation (MI) estimates were derived using Rubin's combining rule. Baseline value based on run-in diaries from Study 3003.
Presented proportions are based on subjects in the FAS-Ext or FAS-Ext-I and randomized treatment. Weeks are relative to start of double-blind treatment in Study 3003.
[a] OAB Wet only.
Source: Study 3004 CSR, Tables 14.2.6.1, 14.2.9.1, 14.2.5.1, Table 14.2.11.1 with reviewer edits

Dose/Dose Response

Single 75mg daily dose studied in both Studies 3003 and 3004.

Durability of Response

This study was a randomized, double-blind, active-controlled, long-term extension to 52 weeks with results representing durability of response up to 52 weeks.

Persistence of Effect

Persistence of effect was not studied formally for vibegron in any of the pivotal phase 3 studies.

Additional Analyses Conducted on the Individual Trial

Not Applicable

6.3.Merck Study 008: Phase 2b Study Supportive Study

6.3.1. Study Design

Overview and Objective

Merck Study 008 is a supportive study for this NDA as This Phase 2 study tested different doses (50 mg and 100 mg daily vs 75 mg daily in Study 3003/3004), had a different length of exposure (8 weeks vs 12 weeks in Study 3003), and had a different patient voiding diary (slightly different questions for urge incontinence and urgency).

The Sponsor used efficacy data from Merck Study 008 to define the responder percentage endpoints and final dosage of 75mg daily in studies 3003/ 3004.

Title: A Phase IIb, Randomized, Placebo- and Active Comparator (Tolterodine)-Controlled, 2-Part, Clinical Study of the Efficacy and Safety of MK-4618 in Patients with Overactive Bladder (Merck Study 008)

Objective: Objectives depended on study period (i.e., Base Study or Extension Study) as follows:

Primary Objectives (Base Study)

- To investigate a dose-related reduction in average daily number of micturitions compared with placebo at Week 8
- To assess the safety and tolerability of treatment with the selected vibegron doses either alone or dosed concomitantly with tolterodine ER

Secondary Objectives (Base Study)

- After 8 weeks of dosing, to assess the effect of vibegron compared with the effect of placebo on:
  - the average number of UUI episodes in subjects with OAB Wet
  - the average number of total urinary incontinence episodes in subjects with OAB Wet
  - the average number of urgency episodes in all subjects with OAB
- To investigate whether there is a lower incidence of dry mouth when treated with vibegron compared with tolterodine ER
- After 4 weeks of dosing, to assess the effect of concomitant dosing with vibegron and tolterodine ER compared with the effect of the selected dose of vibegron

monotherapy and with the effect of tolterodine ER monotherapy on the average daily number of micturitions

Primary Objectives (Extension Study)

- To assess the long-term safety and tolerability of treatment with vibegron compared to tolterodine ER
- To assess the long-term safety profile of vibegron dosed concomitantly with tolterodine ER, relative to vibegron monotherapy and/or tolterodine ER monotherapy

Secondary Objectives (Extension Study)

- To assess the efficacy profile of vibegron compared with tolterodine ER after 52 weeks of treatment in terms of:
  - the average daily number of micturitions in all subjects with OAB
  - the average daily number of UUI episodes in subjects with OAB Wet
  - the average daily number of total urinary incontinence episodes in subjects with OAB Wet
  - the average daily number of urgency episodes in all subjects with OAB
  - average single voided volume
  - quality-of-life domain score based on King's Health Questionnaire

Of note, the definitions used for UUI and urgency episodes in Study 008 were consistent with definitions used in Studies 3003/3004.

Trial Design

Study 008 was a 2-part, randomized, double-blind, placebo- and active-controlled (tolterodine ER 4 mg), parallel-group study of vibegron in men and women with OAB (stratified as OAB Wet and OAB Dry based on responses in a Voiding Diary). Eligible subjects had an average of ≥ 8 micturitions per day. Subjects in the OAB Wet stratum had an average ≥ 1 incontinence episodes ≥ 1 per day. Subjects in the OAB Dry stratum had an average of ≥ 3 urgency episodes and an average of < 1 urgency incontinence episodes per day. The total number of urgency incontinence episodes must have exceeded the total number of stress incontinence episodes for all subjects.

Part 1 was a dose-ranging study to assess the safety, tolerability, and efficacy of vibegron and a proof of concept study for concomitant dosing of vibegron with tolterodine ER 4 mg.

Part 2 was designed to continue to assess the safety and efficacy of vibegron alone as well as the concomitant dosing of vibegron and tolterodine ER. Subjects who completed participating in the initial randomized study phases (Parts 1 and 2) had the option of enrolling in a 52-week

extension (Study 008 Extension). Study treatments are described in the following table.

Table 36: Study 008 Treatments in Part 1, 2, and Extension

Randomized Base Study Treatment	Assigned Extension Study Treatment[c](N = 845)
Part 1[a](N = 987)	
Vibegron 3 mg (n = 144)	Vibegron 50 mg
Vibegron 15 mg (n = 134)	Vibegron 100 mg
Vibegron 50 mg (n = 150)	Vibegron 50 mg
Vibegron 100 mg (n = 149)	Vibegron 100 mg
Tolterodine ER 4 mg (n = 135)	Tolterodine ER 4 mg
Placebo (n = 141)	Tolterodine ER 4 mg
Vibegron 50 mg + tolterodine ER 4 mg for 4 weeks followed by vibegron 50 mg for 4 weeks (n = 134)	Vibegron 50 mg
Part 2[b](N = 408)	
Vibegron 100 mg (n = 112)	Vibegron 100 mg
Tolterodine ER 4 mg (n = 122)	Tolterodine ER 4 mg
Vibegron 100 mg + tolterodine ER 4 mg (n = 110)	Vibegron 100 mg + tolterodine ER 4 mg
Placebo (n = 64)	Vibegron 100 mg + tolterodine ER 4 mg

Notes: All study treatment dosing was once daily. Part 1 dosing was 8 weeks for each product unless otherwise noted. Part 2 dosing was for 4 weeks. Extension Treatment dosing was for 52 weeks

a Subjects in Part 1 were equally randomized to one of the 7 base study treatments indicated.
b Subjects in Part 2 were randomized in a 2:2:2:1 ratio, to one of the 4 base study treatments indicated, respectively for the order listed
c Combined treatment group numbers for extension study were n = 223 for vibegron 50 mg; n = 248 for vibegron 100 mg; n = 240 for tolterodine ER 4 mg; and n = 134 for Vibegron 100 mg + tolterodine ER 4 mg

Source: Merck Study 008 CSR Synopsis

6.3.2. Study Results

Patient Disposition

Study Population: Of the 1395 subjects randomized, 1124 (80.6%) were in the OAB Wet stratum and 271 (19.4%) were in the OAB Dry stratum. The study population was predominantly female (89.7%). The median age was 59.0 years. Most subjects were white (68.5%) or Asian (24.1%). Approximately one-third (36.7%) of subjects had received prior anticholinergic treatment for OAB. There were no clinically meaningful differences between treatment groups with respect to demographics or baseline characteristics, including baseline OAB characteristics. Demography and baseline characteristics also were generally consistent when assessed for the subgroup of subjects who continued into the Extension Study.

Efficacy Results

Key efficacy endpoint data for the 8-week Part 1 portion of the study include endpoints of CFB

at Week 8 for the daily number of micturitions, UUI episodes, urgency episodes, total urinary incontinence episodes, and volume per micturition.

Efficacy analyses used a constrained longitudinal data analysis (cLDA) model that included terms for time, region, study part, and interaction of time by treatment.

Primary Efficacy Endpoint: Micturitions
Treatment with vibegron 50 mg or 100 mg once daily resulted in highly statistically significant and dose-dependent reductions from baseline at Week 8 in average daily number of micturitions (p = 0.007 and 0.000 for the 2 doses, respectively). The following table summarizes these results.

Table 37: Study 008 (Part 1) Primary Efficacy Endpoint-CFB Micturition Average Daily Week 8

	Placebo	Vibegron 50 mg	Vibegron 100 mg	Tolterodine ER
Baseline Daily Number of Micturitions				
n	141	148	148	134
Mean (SD)	10.86 (2.84)	11.21 (3.16)	11.15 (2.32)	11.00 (2.17)
Change from Baseline at Week 8 in Average Daily Number of Micturitions				
LS means (95% CI)	-1.16 (-1.50, -0.82)	-1.80 (-2.13, -1.47)	-2.07 (-2.40, -1.74)	-1.71 (-2.05, -1.36)
Active – Placebo				
LS means difference (95% CI)		-0.64 (-1.11, -0.18)	-0.91 (-1.37, -0.44)	-0.54 (-1.02, -0.07)
P-value		0.007	0.000	0.026

CI = confidence interval; cLDA = constrained longitudinal data analysis; LS = least squares; OAB = overactive bladder; SD = standard deviation
Notes: Constrained longitudinal data analysis (cLDA) model included terms for time, region, study part, and interaction of time by treatment.
Source: Study 008 CSR Table 11-2

Secondary Efficacy Endpoints:
Treatment with vibegron 50 mg or 100 mg once daily resulted in highly statistically significant reductions from baseline at Week 8 in average daily number of UUI episodes (p = 0.000 for both doses), which was a secondary efficacy endpoint for the study which is shown in the following table.

Table 38: Study 008 (Part 1): CFB UUI Average Daily Week 8 in OAB Wet Patients

	Placebo	Vibegron 50 mg	Vibegron 100 mg	Tolterodine ER
Baseline Daily Number of UUI Episodes[a]				
n	118	121	122	100
Mean (SD)	3.11 (2.68)	2.81 (2.06)	2.96 (2.42)	2.80 (2.13)
Change from Baseline at Week 8 in Average Daily Number of UUI Episodes[a]				
LS means (95% CI)	-1.24 (-1.52, -0.95)	-1.95 (-2.23, -1.67)	-1.95 (-2.23, -1.67)	-1.69 (-2.00, -1.38)

Active – Placebo			
LS means difference (95% CI)[a]	-0.72 (-1.11, -0.33)	-0.71 (-1.10, -0.32)	-0.46 (-0.87, -0.04)
P-value	0.000	0.000	0.030

CI = confidence interval; cLDA = constrained longitudinal data analysis; CI = confidence interval; LS = least squares; SD = standard deviation; UUI = urge urinary incontinence
Notes: Constrained longitudinal data analysis (cLDA) model included terms for time, region, study part, and interaction of time by treatment.
a Only in OAB Wet subjects.
Source: Study 008 CSR Table 11-3

Urgency Efficacy Endpoint:
Treatment with vibegron 50 mg or 100 mg once daily resulted in statistically significant reductions from baseline at Week 8 in average daily number of urgency episodes (p = 0.024 for vibegron 50 mg and p = 0.000 for vibegron 100 mg), which was another secondary efficacy endpoint for the study, which is shown in the following table.

Table 39: Study 008 (Part 1) CFB Urgency Episode Average Daily OAB Wet Patients Week 8

	Placebo	Vibegron 50 mg	Vibegron 100 mg	Tolterodine ER
Baseline Daily Number of Urgency Episodes				
n	141	148	148	134
Mean (SD)	6.52 (4.37)	6.43 (4.22)	7.34 (4.14)	6.39 (3.78)
Change from Baseline at Week 8 in Average Daily Number of Urgency Episodes				
LS means (95% CI)	-1.59 (-2.07, -1.11)	-2.36 (-2.82, -1.89)	-2.83 (-3.30, -2.37)	-2.53 (-3.03, -2.04)
Active – Placebo				
LS means difference (95% CI)		-0.76 (-1.43, -0.10)	-1.24 (-1.90, -0.58)	-0.94 (-1.62, -0.26)
P-value		0.024	0.000	0.007

CI = confidence interval; cLDA = constrained longitudinal data analysis; CI = confidence interval; LS = least squares; SD = standard deviation; UUI = urge urinary incontinence
Notes: Constrained longitudinal data analysis (cLDA) model included terms for time, region, study part, and interaction of time by treatment.
Source: Study 008 CSR Tables 11-5

6.4.Kyorin Study 301: Japan-based Supportive Study

6.4.1. Study Design

Overview and Objective

Kyorin Study 301 and accompanying extension Kyorin study 302 were conducted in Japan to support registration of vibegron in that country. Because the studies used different dosages and efficacy endpoints, these studies are considered as supportive efficacy studies and will be outlined briefly below.

Title: KRP-114V Phase III Clinical Study - Double-Blind Controlled Study to Examine Efficacy and Safety of KRP-114V in Overactive Bladder Patients (Kyorin Study KRP114V-T301) – Study 301

Objective: The study objective was to examine the efficacy (superiority to placebo) and safety of vibegron (KRP-114V) when administered orally to subjects with OAB for 12 weeks at dosages of 50 mg or 100 mg per day.

Trial Design

Design: Study 301 was a double-blind, randomized, placebo- and active (imidafenacin)-controlled, multi-center, Phase 3 study designed to evaluate the safety and efficacy of vibegron (50 or 100 mg once daily) in Japanese males and females with OAB. The study was the pivotal study to support marketing authorization for vibegron in Japan.

For entry into Study 301, subjects were ≥ 20 years of age and had symptoms of OAB for at least 6 months including (per a urinary diary) an average daily number of micturitions > 8 times and presence of daily UUI frequency and daily urgency, with and a total number of UUI episodes exceeding half of the total number of urinary incontinence reports. Upon completion of the placebo run-in period, subjects were randomized in a 2:2:2:1 ratio to receive blinded study treatment (placebo, vibegron 50 mg, vibegron 100 mg, or imidafenacin 0.2 mg) for 12 weeks. To maintain the study blind, all subjects received study drug twice daily for consistency with standard imidafenacin dosing; however, active vibegron was only administered once daily in the morning with placebo administered in the evening.

Study Endpoints

The primary endpoint was the CFB in the average daily urination frequency at Week 12 of treatment period.

Secondary efficacy and PRO endpoints included CFB at Week 12 in the following items:

- average daily average number of urgency episodes
- average daily UUI episodes
- average daily number of urinary incontinences per day
- average nocturnal urination frequency
- average single voided volume
- quality-of-life domain score based on King's Health Questionnaire
- degree of subjective improvement based on PGI

Safety endpoints included AEs, laboratory tests, vital signs (blood pressure, heart rate), 12-lead electrocardiogram, and residual (post-void) urine volume.

6.4.2. Study Results

Patient Disposition

Study Population: Of the 1459 subjects who entered the study, 1225 completed the placebo run- in and subsequently received at least 1 dose of study drug in the planned treatment evaluation period (371 placebo; 371 vibegron 50 mg; 371 vibegron 100 mg; 117 imidafenacin); 1188 completed the 12-week study period (358 placebo; 361 vibegron 50 mg; 357 vibegron 100 mg; 112 imidafenacin). Of the 1230 who received at least 1 dose of study drug, 1224 overall were in the FAS and were evaluated for efficacy, and 951 were in the FAS for Incontinence (FAS-I).

The study population was predominantly female (~90% across treatment groups), with an average age of approximately 59 years. All subjects were Japanese. Prior use of OAB treatment was present in 16.7% of subjects at study start. There were no clinically meaningful differences between treatment groups with respect to demographics or baseline characteristics, including baseline OAB characteristics.

Efficacy Results – Primary Endpoint
Efficacy analyses used a constrained longitudinal data analysis (cLDA) model that included terms for time, region, study part, and interaction of time by treatment.

Study 301- Primary Efficacy Endpoint: Micturitions
For the primary study endpoint, both doses of vibegron (50 or 100 mg) resulted in highly statistically significant reductions from baseline at Week 12 in average daily number of micturitions. The difference in LS Means from vibegron treatment groups to placebo group was -0.86 episodes ($p < 0.0001$) in vibegron 50-mg group and -0.81 episodes ($p < 0.0001$), showing a statistically significant decrease of the average daily number of micturitions from Week 0 to Week 12 in both vibegron treatment groups compared with the placebo group. The following table summarizes the primary endpoint in Study 301.

Table 40: Study 301 Primary Efficacy Endpoint: Micturitions Average Daily CFB Week 12

	Placebo	Vibegron 50 mg	Vibegron 100 mg	Imidafenacin 0.2mg
Baseline Daily Number of Micturitions				
n	369	370	368	117
Mean (SD)	11.20 (2.40)	11.13 (2.37)	11.08 (2.25)	11.21 (2.17)
Change from Baseline at Week 12 in Average Daily Number of Micturitions				
n	354	360	355	112
LS means (95% CI)	-1.21 (-1.40, -1.03)	-2.08 (-2.27, -1.89)	-2.03 (-2.22, -1.84)	-2.06 (-2.39, -1.73)
Active – Placebo				
LS means difference (95% CI)[a]		-0.86 (-1.12, -0.60)	-0.81 (-1.07, -0.55)	NA[a]
P-value		0.0000	0.0000	NA[a]

cLDA = constrained longitudinal data analysis; LS = least squares; OAB = overactive bladder; SD = standard deviation
Notes: Constrained longitudinal data analysis (cLDA) model included terms for time, region, study part, and interaction of time by treatment.
a LS Means difference not presented for comparison of imidafenacin versus placebo.
Source: Study 301 CSR Table 11.4-1

Key Secondary Endpoint: UUI

Treatment with vibegron at doses of either 50 or 100 mg once daily resulted in highly statistically significant and dose-dependent reductions from baseline at Week 12 relative to placebo in the average daily number of UUI episodes (LS means difference: -0.26 [p = 0.0015] for the vibegron 50 mg group and -0.43, p = 0.0000 for the vibegron 100 mg group). Changes from baseline with vibegron were comparable to those of the active control, imidafenacin 0.2 mg, for reduction in UUI episodes at Week 12 relative to baseline. The following table summarizes UUI changes from baseline at week 12 in study 301 for OAB Wet patients only.

Table 41: Study 301 UUI Average Daily CFB in OAB Wet Patients Week 12

	Placebo	Vibegron 50 mg	Vibegron 100 mg	Imidafenacin 0.2mg
Baseline Average Daily Number of UUI Episodes[a]				
n	285	289	284	93
Mean (SD)	2.12 (1.30)	2.17 (1.47)	2.06 (1.29)	2.31 (1.40)
Change from Baseline at Week 12 in Daily Number of UUI Episodes[a]				
n	275	281	276	88
LS means (95% CI)	-1.23 (-1.37, -1.09)	-1.48 (-1.62, -1.35)	-1.65 (-1.79, -1.52)	-1.65 (-1.88, -1.42)
Active – Placebo				
LS means difference (95% CI)[b]		-0.26 (-0.43, -0.08)	-0.43 (-0.61, -0.25)	NA[b]
P-value		0.0015	0.0000	NA[b]

LS = least squares; NA = not applicable OAB = overactive bladder; SD = standard deviation
Notes: Constrained longitudinal data analysis (cLDA) model included terms for time, region, study part, and interaction of time by treatment.
NOTE: The p-values shown is as conducted for the CSR analyses (ie, to 4 decimals).
a Only in OAB Wet subjects.#
b LS Means difference was not presented for comparison of imidafenacin versus placebo in this study.
Source: Study 301 CSR Table 11.4-2

Secondary Efficacy Endpoint: Urgency

Treatment with vibegron at doses of either 50 or 100 mg once daily also resulted in highly statistically significant and dose-dependent reductions from baseline at Week 12 relative to placebo in the average daily number of urgency episodes (LS means difference: -0.51 [p = 0.0001] for the vibegron 50 mg group and -0.67, p = 0.0000 for the vibegron 100 mg group. Changes from baseline with vibegron were numerically greater than those of the active control, imidafenacin 0.2 mg, for reduction in urgency episodes at Week 12 relative to baseline. The following table summarizes the results of change from baseline in urgency episodes in Study 301 at Week 12.

Table 42: Study 301-CFB Urgency Average Daily Episodes Week 12 FAS

	Placebo	Vibegron 50 mg	Vibegron 100 mg	Imidafenacin 0.2mg
Baseline Average Daily Number of Urgency Episodes				
n	369	370	268	117
Mean (SD)	3.77 (2.23)	3.70 (2.08)	3.77 (2.25)	3.54 (1.91)
Change from Baseline at Week 12 in Daily Number of UUI Episodes[a]				
n	354	360	355	112
LS means (95% CI)	-1.77 (-1.96, -1.58)	-2.28 (-2.46, -2.09)	-2.44 (-2.63, -2.25)	-2.15 (-2.47, -1.82)
Active – Placebo				
LS means difference (95% CI)[a]		-0.51 (-0.76, -0.25)	-0.67 (-0.93, -0.42)	NA[a]
P-value		0.0001	0.0000	NA[a]

cLDA = constrained longitudinal data analysis; LS = least squares; NA = not applicable OAB = overactive bladder; SD = standard deviation
Notes: Constrained longitudinal data analysis (cLDA) model included terms for time, region, study part, and interaction of time by treatment.
NOTE: The p-values shown is as conducted for the CSR analyses (ie, to 4 decimals).
a LS Means difference was not presented for comparison of imidafenacin versus placebo in this study.
Source: Study 301 CSR Table 11.4-2

Other Key Efficacy Endpoints:
Other predefined key OAB secondary endpoints (average daily number of total urinary incontinence episodes and average volume voided per micturition) were statistically significant in favor of vibegron compared with placebo.

6.5. Kyorin Study 302-Japan-Based Extension Study from Study 301

6.5.1. Study Design

Overview and Objective

This extension study from Kyorin 301 was conducted to evaluate the safety and efficacy of long-term administration of vibegron and is a supportive efficacy study based on different doses, patient populations, and study design.

Title: Open-label, non-controlled study to examine the safety and efficacy of long-term administration of KRP-114V in overactive bladder patients (Kyorin Study KRP114V-T302)

Objective: The study objective was to evaluate the safety and effectiveness of long-term (52 week) administration of vibegron (50 mg with possible increase to 100 mg) for OAB.

Trial Design

Study 302 was an open-label (vibegron 50 mg or 100 mg), long-term (52-week) safety and efficacy study. Upon study entry, all subjects were to receive vibegron 50 mg once daily; after 8

weeks of open-label administration of the vibegron 50 mg once daily, the dose could be increased to 100 mg once daily at the investigator's discretion (and with subject consent) as clinically indicated. The dose assigned at Week 8 of Study 302 was to be maintained for the duration of the study through Week 52 (ie. an additional 44 weeks of dosing).

Study Endpoints

Efficacy and PRO endpoints included CFB at Week 52 in the following items:

- average daily micturition frequency
- average daily urgent urinary frequency
- average daily UUI episodes
- average number of urinary incontinences per day
- average nocturnal urination frequency
- average single voided volume
- quality-of-life domain score based on King's Health Questionnaire
- degree of subjective improvement based on PGI

6.5.2. Study Results

Patient Disposition

In the study, a total of 167 subjects were treated with vibegron across 25 clinical study sites in Japan. (Note that 2 subjects were enrolled at multiple sites, thus, although 169 subjects were enrolled, only 167 unique subjects were treated.) One-hundred eighteen subjects maintained a 50-mg dose throughout the study and 51 subjects increased to a 100-mg dose once daily after eight weeks. Nineteen subjects discontinued the study prematurely. The overall demographics were consistent with those of Study 301.

Protocol Violations/Deviations

2 patients enrolled at multiple sites. See notation above under Patient Disposition.

Demographic Characteristics

The overall demographics were consistent with those of Study 301. Approximately 90% of subjects were female, and the mean age was approximately 60 years.

Efficacy Results – Primary Endpoint

The results of Study 302 demonstrate once daily vibegron maintains statistically and clinically significant improvement over a 52-week treatment period relative to baseline in symptoms of OAB including the prespecified efficacy endpoints of daily number of micturitions, UUI episodes, and urgency episodes.

Other prespecified efficacy endpoints (total urinary incontinence episodes and total volume per void) also showed sustained improvement for vibegron relative to baseline through 52 weeks of treatment.

Vibegron, whether maintained at a dose of 50 mg or increased to a dose of 100 mg, resulted in statistically significant reductions from baseline at Week 52 in all of these endpoints. These results confirm the durability of vibegron efficacy with chronic administration.

Durability of Response

Study 302 showed that vibegron at either 50 or 100 mg had durable effect with chronic administration.

Persistence of Effect

Not Applicable.

7. Integrated Review of Effectiveness

7.1.Assessment of Efficacy Across Trials

Assessment of efficacy across 1) the Urovant pivotal study 3003, 2) the randomized, double-blind, active-controlled, safety extension Urovant study 3004, 3) the 8-week, randomized, double-blind, placebo- and active-controlled, Phase 2b Merck study 008, and 4) the 12-week, randomized, double-blind, placebo- and active-controlled, Phase 3 Kyorin 301 conducted in Japanese patients was consistent, demonstrating statistically significant but small effects of vibegron compared to placebo on daily number of micturitions and daily number of UUI. For most of the secondary efficacy endpoints, which are described in detail in the 4 study synopses in Section 6, vibegron also showed statistically significant but small effects compared to placebo.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Lacking an effect on blood pressure, vibegron may have greater use in OAB patients with hypertension/pre-hypertension, as well as in OAB patients of older age, which comprise a large

percentage of OAB product users in general.

7.2.2. Other Relevant Benefits

Single-dose vibegron 75mg daily does not need titration for efficacy.

7.3. Integrated Assessment of Effectiveness

The Sponsor has submitted evidence of effectiveness that meets the statutory evidentiary standard.

The following summary bullets described results from the Phase 3 Urovant study 3003, which was the only efficacy and safety study that tested the 75 mg daily dose for 12 weeks in a typically representative OAB population. The other large studies were supportive for effectiveness as the Phase 2b Merck Study 008 tested daily doses of 3 mg, 15 mg, 50 mg and 100 mg for 8 weeks, while the Phase 3 Kyorin Study 301 tested daily doses of 50mg and 100 mg for 12 weeks in Japanese patients only. The efficacy results for these supportive studies are described in Section 6 and are not repeated here.

- Study 3003 studied 1518 patients who were randomized to vibegron 75 mg daily dose, placebo and active-control tolterodine.
- A large placebo response was present across all primary and secondary efficacy endpoint results, consistent with other OAB studies in this patient population.
- The following table summarizes the results for the co-primary endpoints of average daily micturitions and average daily urge urinary incontinence (UUI) and key secondary endpoint of urgency (need to urinate immediately) which all met statistical significance but the difference from placebo in each endpoint was small (between -0.5 to -0.7 episodes mean differences from placebo).
- Of note, "urgency" has been a difficult term to precisely define or characterize in clinical studies resulting in most OAB studies relying on more objective measures, such as number of micturitions and UUI. Based on data from qualitative studies as well as preliminary quantitative evidence from the Merck Phase 2b Study 008, the Sponsor used the term "need to urinate immediately" in the patient voiding diary (PVD) in Study 3003 to define both the UUI and urgency episode endpoints from the patient's perspective. The use of the term "need to urinate immediately" for "urgency" is novel and has not been used previously to support approval of other OAB products

Parameter	Placebo	Vibegron 75 mg
Average Daily Number of Micturitions-Co-Primary Endpoint		
Baseline mean (n)	11.75 (520)	11.31 (526)
Change from Baseline▪ (n)	-1.3 (475)	-1.8 (492)

Difference from Placebo	-0.5	
95% Confidence Interval	-0.8 to -0.2	
p-value	<0.001	
Average Daily Number of UUI Episodes-Co-Primary Endpoint		
Baseline mean (n)	3.49 (405)	3.43 (403)
Change from Baseline▪ (n)	-1.4 (372)	-2.0 (383)
Difference from Placebo	-0.6	
95% Confidence Interval	-0.9 to -0.3	
p-value	<0.0001	
Average Daily Number of Urgency Episodes-Key Secondary Endpoint		
Baseline mean (n)	8.13 (520)	8.11 (526)
Change from Baseline▪ (n)	-2.0 (475)	-2.7 (383)
Difference from Placebo	-0.7	
95% Confidence Interval	-1.1 to -0.2	
p-value	0.0020	
▪ Least squares mean adjusted for treatment, baseline, sex, geographical region, study visit, and study visit by treatment interaction term		

The Division of Clinical Outcomes Assessment (DCOA) analyzed the results for these three endpoints using anchor-based methods to estimate "clinical meaningful" within-patient change thresholds. Based on their analyses, DCOA determined:

- For the Co-Primary Endpoint-Average Daily Number of Micturition: Cumulative distribution function curve representation of the data showed minimal separation between the treatment and placebo arms.
- For the Co-Primary Endpoint-Average Daily Number of UUI Episodes: DCOA's anchor-based analysis of the data from Study 3003 suggested that a 90% reduction from baseline in UUI was a clinically meaningful threshold. 35.3% vibegron patients had ≥ 90% reduction in the average daily number of UUI episodes compared to 23.7% of placebo patients.
- For the Key Secondary Endpoint-Urgency (Need to Urinate Immediately): DCOA's anchor-based analysis of the data from Study 3003 suggested that a 60% reduction from baseline in urgency episodes was a clinically meaningful threshold. 33.7% vibegron patients had ≥60% reduction in the average daily number of urgency episodes compared to 28.1% of placebo patients.

8. Review of Safety

8.1.Safety Review Approach

The primary focus of the vibegron safety evaluation is on the data from pivotal Study 3003 and its extension Study 3004, which evaluated the 75-mg daily dose.

Supportive safety data come from 4 other studies:

1) Study 1001: An ambulatory blood pressure monitoring (ABPM) study
2) Merck Study 008: a large, randomized, double-blind, placebo- and active-controlled, Phase 2b, dose-finding study with vibegron
3) Kyorin Study 301: a large, randomized, double-blind, placebo- and active-controlled, Japanese phase 3 study
4) Kyorin Study 302: the extension study to Kyorin Study 301

The following table outlines these vibegron safety studies.

Table 43: Vibegron Safety Data from Clinical Studies in OAB Patients

Study No. Phase; Sponsor; Region	Design; Population	Status	Vibegron Regimen Evaluated	Number of Subjects Treated			
				Vibegron	Comparator	Placebo	Total
Key Studies							
3003 Phase 3; Urovant; Global	Double-blind, randomized, placebo- and active-controlled, multicenter parallel-group study; following a 2-week placebo run-in period, subjects were randomized 5:5:4 to receive blinded treatment of vibegron, placebo, or tolterodine ER Adults with wet or dry OAB	Complete	Vibegron 75 mg, tolterodine ER 4 mg, or placebo administered orally once daily for 12 weeks	545	430	540	1515
3004 Phase 3; Urovant; United States	Double-blind, randomized, active-controlled, 40-week extension study for subjects who completed Study 3003; subjects randomized to vibegron or tolterodine ER in Study 3003 continued the same blinded treatment during Study 3004; subjects randomized to placebo in Study 3003 were re-randomized to vibegron or tolterodine ER (1:1) in Study 3004.	Complete	Vibegron 75 mg or tolterodine ER 4 mg, administered orally once daily for 40 weeks	273[a]	232[a]	NA	505[a]
Supportive Studies							
1001 Phase 1; Urovant; United States	Double-blind, randomized, placebo-controlled, parallel study of the effect of vibegron on 24-hour blood pressure and heart rate. Adults with overactive bladder, aged 40 to 75 years	Complete	Vibegron 75 mg or matched placebo administered orally once daily for 4 weeks	106	NA	108	214

Study No. Phase; Sponsor; Region	Design; Population	Status	Vibegron Regimen Evaluated	Number of Subjects Treated			
				Vibegron	Comparator	Placebo	Total
008 Phase 2; Merck; Global	Double-blind, randomized, placebo- and active comparator (tolterodine ER)-controlled, 2-part efficacy and safety study with 52-week extension Adults with overactive bladder; Part 1: aged 18 to 75 years; Part 2: aged 18 to 75 years Extension: subjects completing either Part 1 of Part 2	Complete	Part 1: vibegron 3 mg, 15 mg, 50 mg, or 100 mg, tolterodine ER 4 mg, or placebo orally, once daily for 8 weeks; or vibegron 50 mg concomitantly with tolterodine ER for 4 weeks followed by 50 mg alone for 4 weeks, orally, once daily Part 2: vibegron 100 mg, tolterodine ER 4 mg, vibegron 100 mg with tolterodine ER 4 mg, or placebo, orally once daily for 4 weeks	931[a]	257[b]	205	1393
			Extension: vibegron 50 mg, vibegron 100 mg, vibegron 100 mg + tolterodine ER 4 mg, or tolterodine ER 4 mg, orally, once daily	605[b]	240[c b]	NA	845
301 Phase 3; Kyorin; Japan	Phase 3, randomized, double-blind, placebo-controlled; Adults with OAB, aged ≥ 20 years	Complete	Vibegron 50 mg (once daily) + placebo; or vibegron 100 mg (once daily) + placebo; or placebo; or imidafenacin 0.2 mg (twice daily) + placebo; orally 12 weeks	739	117	369	1225
302 Phase 3; Kyorin; Japan	Phase 3, open-label, safety and efficacy study; Adults with OAB, aged ≥ 20 years	Complete	Vibegron 50 mg (once daily, orally) for 8 weeks, then either vibegron 50 mg or 100 mg (once daily, orally) for 44 weeks	167	NA	NA	167

ER = extended release; NA = not applicable; OAB = overactive bladder

a 183 subjects (92 randomized to the vibegron group; 91 randomized to the tolterodine ER group) were assigned to placebo in Study 3003 and received a total of 40 weeks of vibegron or tolterodine ER; all other subjects received 52 weeks of active study drug (vibegron or placebo) combined for Studies 3003/3004.

b Includes 244 subjects receiving vibegron + tolterodine ER

c Includes only subjects receiving tolterodine ER alone (excludes 244 subjects receiving vibegron + tolterodine ER)

Source: Table 1: SummClinSafety

8.2. Review of the Safety Database

8.2.1. Overall Exposure

3190 subjects received at least 1 dose of vibegron at doses ranging from 2 to 600 mg in Phase 1, 2, and 3 studies as of August 1, 2020, the data cutoff date for the original NDA submission.

565 healthy volunteers participating in 20 Phase 1 clinical studies received vibegron at single doses ranging from 2 to 600 mg, multiple once-daily doses ranging from 25 to 400 mg for 14 days, or once-daily doses of 150 mg for 28 days.

2625 OAB patients received vibegron in the Phase 2b and 3 Studies Merck 008, Kyorin 301, Kyorin 302, Urovant 3003, and Urovant 3004 and in Phase 1 Study 1001 as either monotherapy or in combination with tolterodine. 513 patients received monotherapy vibegron 75 or 100 mg for ≥ 24 weeks, and 305 subjects received monotherapy vibegron 75 or 100 mg for ≥ 52 weeks.

For duration of treatment in OAB patients, the following table summarizes patient exposure to vibegron 75 or 100 mg as monotherapy in Studies 1001, 3003, 3004, 301, 302, and 008.

Table 44: Duration Exposure to Vibegron 75mg or 100 mg in OAB Patients

	≥ 1 Dose	≥ 24 Weeks	≥ 52 Weeks
Vibegron 75 mg	651	252	131
Vibegron 100 mg	681[a]	261	174
Total	1332	513	305

Includes data from Studies 1001, 3003, 3004, 301, 302, and 008 and excludes combination therapy
a Includes 630 subjects from Pool 2 Studies (ISS Table 2.1b) plus 51 subjects from Study 302 who increased dose to 100 mg (Study 302 CSR Figure 14.1-1)
Source: ISS Table 2.1c, ISS Table 2.1b, Study 302 CSR Figure 14.1-1 ISS = integrated summary of safety with reviewer edits

8.2.2. Relevant characteristics of the safety population:

The study demographics and baseline disease characteristics are described for each individual study in Section 6.

8.2.3. Adequacy of the safety database:

The safety database and extent of exposure, as described in the previous sections, are adequate to support the NDA for vibegron for treatment of OAB. Study 3003 and its extension Study 3004 are adequate studies to consider for the safety of the 75 mg daily dose, especially

when considering the extensive safety data from doses up to 600 mg in Phase 1 studies and up to 100 mg daily in large, Phase 2b and Phase 3 studies. For studies 3003 and 3004, the study sizes, durations, patient demographics and disease characteristics are appropriate for investigation of the 75mg daily dose. The supportive safety studies included different dosages and patient populations outside the US and these studies contribute data to the overall safety database.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no major issues identified for data integrity or related to the submission itself which had an effect on the safety review.

8.3.2. Categorization of Adverse Events

AEs were coded or recoded from earlier studies using MedDRA (v21.1 or higher). Summaries of AEs focused on treatment-emergent AEs. For pools without subjects re-enrolling into an extension study, the treatment-emergent flags defined in the study CSR were used. For pools with subjects re-enrolling into an extension study, a TEAE was defined as any AE that began or worsened in severity on or after the first dose of the base study treatment specific to each pool through 28 days after the last dose in the extension study. Unless otherwise stated in this document, use of the term "AE" refers to a treatment-emergent AE.

The following AEs were summarized:

- Common AEs, including most frequently reported (≥ 2% for vibegron 75 mg and > placebo, if applicable; and ≥ 1% for vibegron 75 mg and > placebo, if applicable)
- Treatment-related AEs
- Severe or worse AEs (ie, ≥ Grade 3)
- Severe or worse treatment-related AEs
- SAEs
- Treatment-related SAEs
- Fatal AEs
- AEs leading to treatment discontinuation
- Predefined AE of Special Interest categories, as follows:
  - potential major adverse cardiac and cerebrovascular events (MACCE)
  - hypertension

  - orthostatic hypotension
  - cystitis or urinary tract infection
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations requiring withholding or discontinuation of study drug
- Treatment-related AE of Special Interest categories
- Nonfatal SAEs
- AEs of hypertension summarized by pre-existing hypertension status (yes/no).

Severity and relationship to study medication were mapped to consistent terminology (severity: mild, moderate, severe or worse; relationship: related, not related) due to inconsistent terminology used across studies. For pools with placebo-controlled studies, the percentage of AEs occurring in ≥ 1% of the vibegron 75-mg group were plotted with risk difference and 95% confidence interval (CI). A plot was also generated for AEs occurring in ≥ 2% of the vibegron 75-mg group.

AEs of hyperglycemia and anemia were further evaluated as events of special interest in Study 3004.

For each subgroup, AEs were summarized overall (in descending order of PT in the vibegron 75-mg arm) and by most frequently reported (≥ 2% vibegron 75 mg and > placebo, if applicable).

The following table summarizes AE and data exposure subgroups.

Table 45: Subgroups for AE and Exposure Data

Subgroup	**Definition**
Age	< 65 years, ≥ 65 years; < 75 years, ≥ 75 years; < 65 years, ≥ 65 years to < 75 years, ≥ 75 years
At risk age group	≥ 75^{th} percentile using all subjects in a pool
Sex	Male, Female
Race	White, Black or African American, Asian, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino
Diabetes Mellitus at baseline	Yes, No (assessed from the medical history)
Region	US, Non-US
BMI at baseline	≤ 30 kg/m^2, > 30 kg/m^2
Low weight at baseline	≤ 25^{th} percentile using all subjects in a pool

At risk eGFR group	≤ 25th percentile using all subjects in a pool
AE subgroup only: Pre-existing hypertension	Yes, No (based on medical history and/or baseline hypertension per blood pressure data, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg)

8.3.3. Routine Clinical Tests

Laboratory Data

Hematology and clinical chemistry data were summarized using absolute (observed) value and change from baseline. The number and percentage of subjects with laboratory measurements outside of the central laboratory normal range were also summarized. Shift tables from baseline to maximum postbaseline value, to minimum postbaseline value, and at each postbaseline visit were generated.

Increases in ALT, AST, total bilirubin, and alkaline phosphatase were summarized according to the following pre-determined criteria:

- ALT ≥ 3, 5, 10, and 20 x the upper limit of normal (ULN)
- AST ≥ 3, 5, 10, and 20 x the ULN
- AST or ALT ≥ 3, 5, 10, and 20 x the ULN
- total bilirubin > 2 x ULN
- alkaline phosphatase > 1.5 x ULN
- Elevation of AST or ALT ≥ 3 x ULN accompanied by elevated total bilirubin > 1.5 x ULN and > 2 x ULN
- Hy's law: AST or ALT ≥ 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN

In addition, scatter plots were generated for maximum postbaseline ALT/ULN vs baseline ALT/ULN and for maximum postbaseline ALT/ULN vs maximum postbaseline total bilirubin/ULN.

Vital signs

Studies 3003 and 3004 collected blood pressure in triplicate, and Study 1001 collected blood pressure and heart rate at study visits in triplicate which were averaged for analysis. Study 1001 also collected ambulatory blood pressure and heart rate. Vital signs measured in the seated position were used for summaries and analyses except for Study 008, in which both sitting and semi-recumbent positions were used.

Blood pressure and heart rate data from studies measuring blood pressure in triplicate were analyzed separately from studies with single random measurements in addition to being included in the integrated data. The following table summarizes the at-risk subgroups for vital signs.

Table 46: At-Risk Subgroups for Vital Sign Summaries

Subgroup	Definition
Age	≥ 75th percentile using all subjects in a pool and the complement (< 75th percentile)
Pre-existing hypertension	based on medical history and/or baseline hypertension per blood pressure data, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and the complement (no pre-existing hypertension)
Low weight at baseline	≤ 25th percentile using all subjects in a pool and the complement (> 25th percentile)
Renal impairment at baseline	eGFR ≤ 25th percentile using all subjects in a pool and the complement (> 25th percentile)

PVR

Post void residuals (PVR) data were summarized by visit, maximum value, and last postbaseline value for each subject. PVR data were also summarized categorically, using the following levels: < 100 mL, ≥ 100 and < 200 mL, ≥ 200 and < 350 mL, and ≥ 350 mL. PVR were summarized in each subgroup studied. The following table summarizes the subgroup analyses for PVR.

Table 47: Subgroup Analysis for PVR

Subgroup	Definition
Benign prostate hyperplasia at baseline (male subjects only)	Yes, No (based on medical history)

8.4. Safety Results

8.4.1. Deaths

Three deaths were reported in vibegron OAB studies: two patients on vibegron, one patient on active-control tolterodine.

The following are brief narrative summaries on the 2 patient deaths on vibegron. For these two cases, full narratives from the NDA are provided in Appendix 13.3:

1) A 63-year-old female patient [Subject (b) (6)] on vibegron 75 mg in Study 3004 died (b) (6) days after initiating study drug. The subject was enrolled in the 40-week vibegron group after receiving placebo in Study 3003 for 12 weeks. No relevant medical history or other AEs were reported. Throughout the study, the subject had normal vital signs and was not taking any concomitant medications. The death certificate listed arteriosclerotic disease as the cause of death without autopsy. The death was coded as fatal AE of arteriosclerosis.

2) A 69-year-old female patient [Subject (b) (6)] on vibegron 50 mg in Kyorin Study 302 (Japan extension study) died approximately (b) (6) days after initiating study drug in Study 302. The date is approximate (b) (6) and her fall was considered an accident. The death was attributed to cervical spinal cord injury resulting from a fall.

One patient death was on tolterodine in Study 3003:

3) A 75-year-old female patient[Subject (b) (6)] on tolterodine in Study 3003 died (b) (6) days after initiating study drug. The subject had fatal AEs of urinary tract infection, sepsis, and cerebrovascular accident around the time of the death. The main cause of death was assessed as cerebrovascular accident.

8.4.2. Serious Adverse Events

For patients in double-blinded Phase 3 studies 3003 and Kyorin 301, the pooled subject incidence of SAEs was low across all treatment groups (1.0% placebo, 1.5% vibegron 75 mg, 2.3% tolterodine, 0.3% vibegron 100 mg). SAEs reported in > 1 subject were cerebrovascular accident, which was reported in 1 subject receiving vibegron 75 mg and 1 subject receiving tolterodine, and pneumonia, which was reported in 1 subject receiving placebo and 1 subject receiving vibegron 75 mg). In addition to cerebrovascular accident and pneumonia, SAEs reported in the vibegron 75-mg treatment group were abdominal pain, appendix disorder, atrial fibrillation, cardiac failure congestive, colitis, colorectal adenocarcinoma, noncardiac chest pain, and pleural effusion (1 subject [0.2%] each).

Two subjects, both in the vibegron 75-mg group, had SAEs (noncardiac chest pain and pneumonia, respectively). Both events resolved (both cases in Study 3003 Subjects (b) (6) and (b) (6)).

The following table summarizes the SAEs reported in the 12-week studies, Study 3003 and Kyorin Study 301 which had 1 or more patients in more than one category.

Table 48: SAEs Reported in >1 Subject in Studies 3003 and 301, 12-Week Studies by Dose

	Placebo (N=909) n (%)	Vibegron 75 mg (N=545) n (%)	Tolterodine ER 4 mg (N = 430) n (%)	Vibegron 100 mg (N = 369) n (%)
Any SAE	9 (1.0)	8 (1.5)	10 (2.3)	1 (0.3)
Cerebrovascular	0	1 (0.2)	1 (0.2)	0
Pneumonia	1 (0.1)	1 (0.2)	0	0

ER = extended release; ISS = integrated summary of safety; SAE = serious adverse event
Notes: Adverse events are coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities coding dictionary version 21.1. Subject is counted only once in each preferred term.
Source: ISS Table 2.18a with reviewer edits

Other pooled SAE results were low across treatment groups and consistent with studies 3003 and 301.

For SAE's in the long-term extension pool of Studies 3004, 302, and 008, 9 subjects (3.3%) receiving vibegron 75 mg, 29 subjects (6.1%) receiving tolterodine, and 8 subjects (2.7%) receiving vibegron 100 mg had SAEs.

SAEs reported in > 1 subject overall were appendicitis, breast cancer, chest pain, and pneumonia. SAEs reported in the vibegron 75-mg group were angina unstable, appendicitis, arteriosclerosis, breast cancer, chest pain, colitis, colitis microscopic, pelvic fracture, and urosepsis (each 1 subject [0.4%])

The following table summarizes the SAEs reported in long-term studies.

Table 49: SAEs in Long-term Studies 3004, 302, and 008 reported in > 1 Patient Overall

	Vibegron 75 mg (N = 273) n (%)	Tolterodine ER 4 mg (N = 472) n (%)	Vibegron 100 mg (N = 299) n (%)	Vibegron 75 and 100 mg (N = 572) n (%)
Any SAE	9 (3.3)	29 (6.1)	8 (2.7)	17 (3.0)
Appendicitis	1 (0.4)	2 (0.4)	0	1 (0.2)
Breast cancer	1 (0.4)	1 (0.2)	1 (0.3)	2 (0.3)
Chest pain	1 (0.4)	1 (0.2)	0	1 (0.2)
Pneumonia	0	2 (0.4)	0	0

ER = extended release; ISS = integrated summary of safety; SAE = serious adverse event
Notes: Adverse events are coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities coding dictionary version 21.1. Subject is counted only once in each preferred term.
Source: ISS Table 2.18c with reviewer edits.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The subject incidence of SAEs, severe or worse AEs, fatal AEs, and AEs leading to treatment discontinuation was low among subjects receiving vibegron 75 mg in both studies 3003 and 3004.

In Study 3003, AEs leading to discontinuation included headache (n=3. 0.6% for vibegron 75 mg), hypertension (n=1, 0.2% for vibegron 75mg), nausea (n=1, 0.2% for vibegron 75 mg), palpitations (n=1, 0.2% for vibegron 75 mg), rash (n=1, 0.2% for vibegron 75 mg), diarrhea (no cases for vibegron), dry mouth (no cases for vibegron), fatigue (no cases for vibegron), and somnolence (no cases for vibegron).

Within the vibegron group, headache led to discontinuation of study drug for 3 subjects; no other individual preferred term was reported as an AE leading to discontinuation by more than 1 vibegron 75 mg subject. The rate of discontinuation due to an AE was highest in the tolterodine group, with dry mouth being the most common reason for AE- related discontinuations (n=4, 0.9% for tolterodine ER 4 mg).

The following table summarizes Study 3003 AEs leading to discontinuation.

Table 50: AE Leading to Discontinuation Study 3003 SAF

System Organ Class Preferred Term	Placebo N = 540 n (%) [# AEs]	Vibegron 75 mg N = 545 n (%) [# AEs]	Tolterodine ER 4 mg N = 430 n (%) [# AEs]
Any AE leading to discontinuation of study drug	**6 (1.1) [16]**	**9 (1.7) [16]**	**14 (3.3) [27]**
Gastrointestinal disorders	**1 (0.2) [1]**	**2 (0.4) [2]**	**8 (1.9) [10]**
Dry mouth	0	0	4 (0.9) [4]
Diarrhea	0	0	2 (0.5) [2]
Nausea	1 (0.2) [1]	1 (0.2) [1]	0
Abdominal mass	0	0	1 (0.2) [1]
Abdominal pain	0	0	1 (0.2) [1]
Constipation	0	0	1 (0.2) [1]
Dyspepsia	0	1 (0.2) [1]	0
Gastroesophageal reflux disease	0	0	1 (0.2) [1]
Nervous system disorders	**2 (0.4) [2]**	**5 (0.9) [5]**	**4 (0.9) [6]**
Headache	1 (0.2) [1]	3 (0.6) [3]	2 (0.5) [2]
Cerebrovascular accident	0	1 (0.2) [1]	1 (0.2) [1]

Balance disorder	0	0	1 (0.2) [1]
Cognitive disorder	0	0	1 (0.2) [1]
Dizziness	0	0	1 (0.2) [1]
Migraine	0	1 (0.2) [1]	0
Somnolence	1 (0.2) [1]	0	0
Cardiac disorders	**0**	**2 (0.4) [3]**	**1 (0.2) [1]**
Palpitations	0	1 (0.2) [1]	1 (0.2) [1]
Atrial fibrillation	0	1 (0.2) [1]	0
Bradycardia	0	1 (0.2) [1]	0
General disorders and administration site conditions	**1 (0.2) [2]**	**0**	**2 (0.5) [2]**
Fatigue	1 (0.2) [1]	0	1 (0.2) [1]
Face edema	0	0	1 (0.2) [1]
Feeling abnormal	1 (0.2) [1]	0	0
Vascular disorders	**2 (0.4) [3]**	**1 (0.2) [1]**	**0**
Hypertension	2 (0.4) [2]	1 (0.2) [1]	0
Flushing	1 (0.2) [1]	0	0
Ear and labyrinth disorders	**1 (0.2) [1]**	**0**	**1 (0.2) [1]**
Vertigo	0	0	1 (0.2) [1]
Vertigo positional	1 (0.2) [1]	0	0
Infections and infestations	**0**	**1 (0.2) [1]**	**1 (0.2) [2]**
Pneumonia	0	1 (0.2) [1]	0
Sepsis	0	0	1 (0.2) [1]
Urinary tract infection	0	0	1 (0.2) [1]
Investigations	**0**	**1 (0.2) [2]**	**1 (0.2) [1]**
Alanine aminotransferase increased	0	1 (0.2) [1]	0
Aspartate aminotransferase increased	0	1 (0.2) [1]	0
Blood glucose increased	0	0	1 (0.2) [1]
Psychiatric disorders	**0**	**1 (0.2) [1]**	**1 (0.2) [1]**
Depressed mood	0	0	1 (0.2) [1]
Insomnia	0	1 (0.2) [1]	0
Renal and urinary disorders	**0**	**0**	**2 (0.5) [2]**
Bladder pain	0	0	1 (0.2) [1]
Urine flow decreased	0	0	1 (0.2) [1]

Respiratory, thoracic and mediastinal disorders	**1 (0.2) [3]**	**0**	**1 (0.2) [1]**
Cough	1 (0.2) [1]	0	0
Dysphonia	1 (0.2) [1]	0	0
Nasal congestion	1 (0.2) [1]	0	0
Pneumonia aspiration	0	0	1 (0.2) [1]
Skin and subcutaneous tissue disorders	**1 (0.2) [1]**	**1 (0.2) [1]**	**0**
Rash	1 (0.2) [1]	1 (0.2) [1]	0
Eye disorders	**1 (0.2) [2]**	**0**	**0**
Dry eye	1 (0.2) [1]	0	0
Vision blurred	1 (0.2) [1]	0	0
Musculoskeletal and connective tissue disorders	**1 (0.2) [1]**	**0**	**0**
Musculoskeletal chest pain	1 (0.2) [1]	0	0

Note: Descriptions of AEs were coded using MedDRA version 20.1.
Subjects with multiple AEs within the same system organ class and/or preferred term were only counted once within the respective category.
Source: Table 14.3.1.8 with reviewer edits

Long-term Study 3004 Discontinuations

In Study 3004, the incidence of AEs leading to discontinuation of study drug was again low for both treatment groups, with fewer subjects in the overall vibegron group discontinuing compared with the overall tolterodine group. No individual preferred term was reported as an AE leading to discontinuation by more than 1 subject, and thus, there were no discernable patterns of AEs leading to discontinuation for either treatment group.

The following table summarizes Study 3004 AEs leading to discontinuation.

Table 51: Summary of Discontinuations Study 3004 SAF-Ext

System Organ Class/ Preferred Term	Overall Vibegron 75mg N=273 n (%) [# AEs]	Overall Tolterodine ER 4mg N=232 n (%) [# AEs]
Any AE leading to discontinuation of study drug	**4 (1.5) [5]**	**8 (3.4) [17]**
Nervous system disorders	**1 (0.4) [1]**	**2 (0.9) [2]**
Amnesia	1 (0.4) [1]	0
Dizziness	0	1 (0.4) [1]
Headache	0	1 (0.4) [1]
Renal and urinary disorders	**0**	**3 (1.3) [3]**

Acute prerenal failure	0	1 (0.4) [1]
Chronic kidney disease	0	1 (0.4) [1]
Haematuria	0	1 (0.4) [1]
Cardiac disorders	**0**	**2 (0.9) [6]**
Atrial fibrillation	0	1 (0.4) [1]
Cardiac failure	0	1 (0.4) [1]
Cardiomyopathy	0	1 (0.4) [1]
Mitral valve incompetence	0	1 (0.4) [1]
Sinus tachycardia	0	1 (0.4) [1]
Tricuspid valve incompetence	0	1 (0.4) [1]
Gastrointestinal disorders	**2 (0.7) [2]**	**0**
Constipation	1 (0.4) [1]	0
Diarrhea	1 (0.4) [1]	0
Respiratory, thoracic and mediastinal disorders	**0**	**2 (0.9) [2]**
Dyspnea	0	1 (0.4) [1]
Pulmonary embolism	0	1 (0.4) [1]
Eye disorders	**0**	**1 (0.4) [1]**
Dry eye	0	1 (0.4) [1]
Investigations	**1 (0.4) l2J**	**0**
Blood creatinine increased	1 (0.4) [1]	0
Blood urea increased	1 (0.4) [1]	0
Musculoskeletal and connective tissue disorders	**0**	**1 (0.4) [2]**
Intervertebral disc degeneration	0	1 (0.4) [1]
Osteoarthritis	0	1 (0.4) [1]
Vascular disorders	**0**	**1 (0.4) [1]**
Aortic stenosis	0	1 (0.4) [1]

Note: Overall Vibegron 75mg includes subjects who received 52-weeks and 40-weeks Vibegron 75mg, and Overall Tolterodine ER 4mg includes subjects who received 52-weeks and 40-weeks Tolterodine ER 4mg. Only data for subjects on active treatment were included.
Descriptions of AEs were coded using MedDRA version 20.1.
Subjects with multiple AEs within the same system organ class and/or preferred term were only counted once within the respective category.
Source: Table 14.3.1.8 with reviewer edits

Other studies at other doses (e.g., Merck Study 008 and Kyorin Studies 301 and 302) were consistent with the rates of discontinuations due to AEs in Studies 3003 and 3004.

8.4.4. Significant Adverse Events

A summary of AEs for Studies 3003 and 3004 is included here as these studies reflect treatment with the 75mg daily dose in the US OAB patient population for 12 weeks of treatment in Study 3003 and its extension Study 3004 for up to 52 weeks of treatment. In Studies 3003 and 3004, the subject incidence of SAEs, severe or worse AEs, fatal AEs, and AEs leading to treatment

discontinuation was low among subjects receiving vibegron 75 mg in both studies.

The following table summarize AEs in both Studies 3003 and 3004.

Table 52: Summary of Adverse Events Studies 3003 and 3004 - (SAF and SAF-Ext)

	Study 3003 (Up to 12 weeks of Treatment)			Study 3004 (Up to 52 Weeks of Treatment)[a]	
	Placebo N = 540 n (%)	Vibegron 75 mg N = 545 n (%)	Tolterodine ER 4 mg N = 430 n (%)	Vibegron 75 mg N = 273 n (%)	Tolterodine ER 4 mg N = 232 n (%)
Any AE	180 (33.3)	211 (38.7)	166 (38.6)	171 (62.6)	126 (54.3)
Any Treatment-related AE	56 (10.4)	73 (13.4)	68 (15.8)	59 (21.6)	46 (19.8)
Any Severe or Worse AE	8 (1.5)	6 (1.1)	9 (2.1)	10 (3.7)	8 (3.4)
Any Severe or Worse	3 (0.6)	1 (0.2)	2 (0.5)	1 (0.4)	1 (0.4)
Any SAE	6 (1.1)	8 (1.5)	10 (2.3)	9 (3.3)	10 (4.3)
Any Treatment-	0	2 (0.4)	0	1 (0.4)	2 (0.9)
Any Fatal AE	0	0	1 (0.2)	1 (0.4)	0
Any AE lead to discontinue	6 (1.1)	9 (1.7)	14 (3.3)	4 (1.5)	8 (3.4)
Any AECI	40 (7.4)	36 (6.6)	38 (8.8)	41 (15.0)	32 (13.8)
Any Treatment-related AECI	11 (2.0)	7 (1.3)	11 (2.6)	14 (5.1)	10 (4.3)

AE = adverse event; AECI = adverse event of clinical interest; ER = extended release; SAE = serious adverse event; SAF = safety set; SAF-Ext = Safety Set Extension
a: includes 12 weeks in Study 3003 and 40 weeks in Study 3004
Notes: AECIs were those that were marked by the investigator on the case report form as an AECI. If severity was missing then severity was derived as severe (Grade III). If relationship to study drug was missing then relationship to study drug was derived as treatment-related.
Presented frequencies and the denominator used for percentages are based on patients in the SAF or SAF-Ext and the actual treatment received.
In Study 3004, overall vibegron 75 mg includes patients who received 52 weeks and 40 weeks vibegron 75 mg, and overall tolterodine ER 4 mg includes patients who received 52 weeks and 40 weeks Tolterodine ER 4 mg. Only data for patients on active treatment were included.
Source: Study 3003 CSR Table 14.3.1.1, Study 3004 CSR Table 14.3.1.1 with reviewer edits

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In both Study 3003 and Study 3004, the most frequently reported AEs of urinary tract infection (in study 3003, 5.0% vibegron 75 mg vs 6.1% placebo), nasopharyngitis (in study 3003, 2.8% vibegron 75 mg vs 1.7% placebo), headache (in study 3003, 4.0% vibegron 75mg vs 2.4% placebo) diarrhea (in study 3003, 2.2% vibegron 75mg vs 1.1% placebo), upper respiratory tract infection (in study 3003, 2.0% vibegron 75mg vs 0.7% placebo), and nausea (in study 3003, 2.2% vibegron 75mg vs 1.1% placebo) were noted at ≥ 2% subject incidence. The type and incidence of AEs reported was consistent with vibegron data in the supportive studies Merck 008, Kyorin 301 and Kyorin 302.The following tables summarize treatment emergent AEs in Studies 3003 and 3004 respectively.

Table 53: Study 3003: AEs Reported in ≥ 2% Patients on Vibegron 75mg (SAF)

Preferred Term	Placebo N = 540 n (%)	Vibegron 75 mg N = 545 n (%)	Tolterodine ER 4 mg N = 430 n (%)
Any AE	**180 (33.3)**	**211 (38.7)**	**166 (38.6)**
Urinary tract infection	33 (6.1)	27 (5.0)	25 (5.8)
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)
Upper respiratory tract infection	4 (0.7)	11 (2.0)	2 (0.5)

AE = adverse event; ER = extended release; SAF = Safety Set
Notes: Descriptions of AEs are coded using Medical Dictionary for Regulatory Activities version 20.1.
Presented frequencies and the denominator used for percentages are based on patients in the SAF and the actual treatment received.
Patients with multiple AEs within the same Preferred Term are only counted once within the respective category.
Source: Study 3003 CSR Table 14.3.1.14 with reviewer edits

Table 54: Study 3004: AEs Reported in ≥ 2% on Vibegron 75mg (SAF-Ext)

Preferred Term	Vibegron 75 mg N = 273 n (%)	Tolterodine ER 4 mg N = 232 n (%)
Any AE	**171 (62.6)**	**126 (54.3)**
Hypertension	24 (8.8)	20 (8.6)
Urinary tract infection	18 (6.6)	17 (7.3)
Headache	15 (5.5)	9 (3.9)
Nasopharyngitis	13 (4.8)	12 (5.2)
Diarrhea	13 (4.8)	4 (1.7)

Upper respiratory tract infection	10 (3.7)	1 (0.4)
Constipation	10 (3.7)	6 (2.6)
Nausea	10 (3.7)	7 (3.0)
Bronchitis	8 (2.9)	3 (1.3)
Anemia	7 (2.6)	2 (0.9)
Residual urine volume increased	7 (2.6)	3 (1.3)
Hyperglycemia	7 (2.6)	2 (0.9)
Back pain	6 (2.2)	3 (1.3)
Musculoskeletal pain	6 (2.2)	1 (0.4)

AE = adverse event; ER = extended release; SAF–Ext = Safety Set Extension
Notes: Includes cumulative data from Study 3003 for subjects who received vibegron or tolterodine in Study 3003 Overall Vibegron 75 mg includes patients who received 52-weeks and 40-weeks Vibegron 75 mg and Overall Tolterodine ER 4 mg includes patients who received 52-weeks and 40-weeks Tolterodine ER 4 mg. Only data for patients on active treatment were included.
Descriptions of AEs are coded using Medical Dictionary for Regulatory Activities version 20.1.
Presented frequencies and the denominator used for percentages are based on patients in the SAF-Ext and the actual treatment received.
Patients with multiple AEs within the same System Organ Class and/or Preferred Term are only counted once within the respective category.
Source: Study 3004 CSR Table 14.3.1.13 with reviewer edits

8.4.6. Laboratory Findings

No clinically meaningful changes in laboratory data were observed in the vibegron Phase 1 studies and in the integrated Phase 2b or 3 data, no clinically meaningful differences in laboratory results were observed between subjects receiving vibegron and subjects receiving placebo or tolterodine. Few subjects in any pool had increased liver enzymes, and no subjects met the laboratory criteria for Hy's law. The following table summarizes liver function testing in the 12-week double blind pooled studies 3003 and Kyorin 301.

Table 55: Summary Liver Function Testing in Pooled Database from 12-week Double-blind Studies 3003 and 301

	Placebo n/N (%)	Vibegron 75 mg n/N (%)	Tolterodine ER 4mg n/N (%)	Vibegron 100 mg n/N (%)
ALT				
≥ 3 x ULN	3/897 (0.3)	1/537 (0.2)	2/419 (0.5)	0
≥ 5 x ULN	1/897 (0.1)	1/537 (0.2)	0	0
≥ 10 x ULN	0	0	0	0
AST				
≥ 3 x ULN	2/897 (0.2)	1/537 (0.2)	1/419 (0.2)	0
≥ 5 x ULN	0	1/537 (0.2)	0	0

≥ 10 x ULN	0	0	0	0
Total bilirubin				
> 2 x ULN	0	1/526 (0.2)	0	0
Alkaline Phosphatase				
> 1.5 x ULN	5/898 (0.6)	9/537 (1.7)	11/420 (2.6)	6/367 (1.6)
Support Hy's Law				
ALT or AST >= 3 x ULN and TBIL > 2.0 x ULN and ALP < 2 x ULN	0	0	0	0

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ER = extended release; ISS = integrated summary of safety; TBIL = total bilirubin; ULN = upper limit of normal
Source: ISS Table 2.47a with reviewer edits

Post Void Residual Urine
In the pooled 12-week double-blind Studies 3003 and 301, the mean change in PVR urine volume from baseline to Week 12 was similar in the placebo group (1.5 mL) and the vibegron 75-mg group (0.3 mL). At Week 12, most subjects had < 100 mL PVR urine volume (92.7% placebo, 87.3% vibegron 75 mg).

No evidence of a clinically relevant difference in PVR urine volume was observed in subjects with baseline BPH compared with subjects without baseline BPH but the number of patients with BPH was small (n=68).

In long-term studies of 52 weeks of treatment, no clinically relevant increase in PVR urine volume was observed for the vibegron 75-mg group (3.1 mL) compared with tolterodine group (1.3mL).

Among patients with BPH at baseline, the mean change in PVR urine volume from baseline to Week 52 was 15.7 mL in the vibegron 75-mg group and 22.1 mL in the tolterodine group. Among subjects without baseline BPH, the mean change in PVR urine volume from baseline to Week 52 was 0.6 mL in the vibegron 75-mg group and 20.0 mL in the tolterodine group.

Reviewer Comments: ***Study results showed no significant PVR changes from baseline for patients treated with ≥ 75 mg vibegron at week 12 or long-term up to week 52. For patients with BPH and without BPH, there was no difference in PVR from baseline noted although the numbers of male patients were small.***

8.4.7. Vital Signs

The Sponsor conducted Study URO-901-1001, a dedicated ABPM study in 197 patients (FAS

population) with overactive bladder randomized to placebo (n=101) or vibegron 75 mg qd (n = 96) for 28 days. The study included two ABPM visits (at baseline and on day 28) with 3 measurements per hour during the daytime (8a to 10p) and 2 measurements per hour during the night time (10p to 8a). At each ABPM visit, there was an option to repeat the ABPM recording to meet the ABPM validity criteria (< 6 consecutive readings during daytime, < 8 missing readings during daytime and < 20 readings missing overall).

The Divison of Cardiovascular and Renal Products (DCN) was consulted to evaluate vital signs and the ABPM study for vibegron. The DCN consult team concluded that there was no significant effect of vibegron on blood pressure with 75mg daily dose in this study and had the following conclusions:

> *"The effect of vibegron was evaluated in a dedicated ABPM study URO-901-1001, a randomized, placebo-controlled study in OAB patients receiving vibegron 75 mg qd or placebo for 28 days. There were no significant increases in placebo-adjusted mean change from baseline (ΔΔ) in daytime and 24-h average systolic BP, diastolic BP and HR.*
>
> *No significant effects of vibegron on blood pressure (BP) was observed in this ABPM study (1001) as evidenced by an upper bound of 1.7 mmHg for the mean change from baseline in systolic BP.*
>
> *Using the Pooled Cohort Equations, this translates into excluding an excess of 0.2 CV events per 1000 patient years for OAB patients."*

For additional information, refer to the DCN consult, dated May 7, 2020. The following table summarizes the 24-h average parameters from Study 1001:

Table 56: ABPM Study 1001: Point Estimates and the 95% CIs

ABPM parameter	Treatment	Metric	ΔΔ	95% CI
Systolic BP	Vibegron 75 mg qd	24-h average	0.5	(-1.3 to 2.4)
Diastolic BP	Vibegron 75 mg qd	24-h average	-0.3	(-1.5 to 1)
Heart Rate	Vibegron 75 mg qd	24-h average	1	(-0.3 to 2.2)

Source: DCN Consult Study 1001-Table 1 DARRTS May 7, 2020

The DCN consult team made the following labeling recommendation for the Prescribing Information Section 12.2:

12.2 Pharmacodynamics

Blood pressure

In a 4-week randomized, placebo-controlled, ambulatory blood pressure study in OAB patients (~~n=197~~n=200), daily treatment with GEMTESA 75 mg was not associated with (b) (4) -clinically significant changes in blood ~~p~~pressure. (b) (4)

We propose to use the n from the FAS population and to describe the study as being negative.

Consistent with the results from Study 1001, no clinically relevant increases in systolic blood pressure were observed among subjects receiving vibegron 75 mg. Across all pools of data for 75mg vibegron group, the mean increase from baseline in SBP was < 1.0 mmHg.

In Study 3003, no notable differences in systolic blood pressure increases ≥ 15 mmHg at 3 consecutive visits were observed across treatment groups for any at-risk subgroups which were defined as subjects with age ≥ 75th percentile, pre-existing hypertension, body weight ≤ 25th percentile, or eGFR ≤ 25th percentile.

In the pooled long-term Studies 008, 3004, and 302 analysis, no clinically relevant differences in mean systolic blood pressure change from baseline were noted in the vibegron 75 mg group across 52 weeks of treatment and no subjects discontinued due to hypertension.

Reviewer Comments: ***The DCN consult team's assessment was that vibegron 75mg did not affect SBP, DBP, or HR after 12 weeks of vibegron treatment. SBP measurements in Study 3003 and in the supportive studies 008, 3004, and 302 were consistent with the results of the ABPM Study 1001. We will consider the DCN consult team's labeling recommendations for labeling.***

8.4.8. Electrocardiograms (ECGs)

In the Phase 1 thorough QTc study (Study 012), no clinically meaningful effect of vibegron was observed on QTc.

In the Phase 2b and 3 studies, differences in data collection precluded integration of ECG data (Study 008 ECG parameters were collected, but abnormal findings were not differentiated between clinically significant and not clinically significant; in Study 3003, Study 3004, and Study 1001 ECGs were collected to assess eligibility and as needed for safety events; in Study 301 and Study 302, ECGs were collected and assayed as normal vs abnormal and for clinical significance).

In the Japan-based Study 301, the incidence of treatment-emergent ECG abnormalities was low (0.5% placebo, 0.8% vibegron 50 mg, 0.5% vibegron 100 mg, and 0.0% imidafenacin) and similar in the vibegron and placebo groups.

In its Japan-based extension Study 302, clinically significant ECG findings were noted in 3.0% of subjects (5/166 subjects) after initiation of study drug, 3.5% of subjects (4/115 subjects) during maintenance, and 2.0% of subjects (1/51 subjects) after increasing the dose of study drug. Among the 4 subjects with abnormalities during maintenance, 2 (left anterior branch block, mild ST T abnormality) were noted to recover at 52 weeks, 1 had an abnormal ECG pre-study and throughout the study, and 1 (ST elevation) discontinued the study due to angina. The subject with an abnormal ECG (ST decline) after increasing the dose of study drug had the same abnormality on repeat testing, but no subsequent abnormality on further testing, making causality unlikely in this case.

Reviewer Comments: ***The incidence of ECG abnormalities was low during vibegron studies and raises no concerns. These findings are consistent with no effects of vibegron on vital signs during treatment in Study 3003 and 1001. Additional discussion of the AECIs hypertension, hypotension, and MACCE appears in in Section 8.6 Specific Safety Issues.***

8.4.9. QT

The FDA Interdisciplinary Review Team (IRT) was consulted to evaluate the through QT study 012. The IRT concluded that *"no significant QTc prolongation effect of Vibegron was detected in this QT assessment "*and made recommendations for labeling of Section 12.2 Pharmacodynamics. See the IRT Consult Review June 19, 2020 DARRTS.

Study 012 evaluated vibegron in a single dose, randomized, double-blind, placebo and active-controlled, 4-period, crossover, thorough QT (TQT) study in 52 healthy subjects. The highest dose of vibegron evaluated was 400 mg, which covers the worst-case exposure scenario (i.e., 2-fold increase in the presence of strong CYP3A4 inhibitor). The data were analyzed using by-timepoint analysis as the primary analysis, which did not suggest that vibegron is associated with significant QTc prolonging effect in the QTc interval. Moxifloxacin 400 mg treatment provided assay sensitivity as the lower bound of 90% CI of maximum mean increase in QTc values was greater than 5 msec. The following table from the consult summarizes the results.

Table 57: Study 012 The Point Estimates and the 90% CIs

ECG parameter	Treatment	Time	ΔΔQTcF (msec)	90% CI (msec)
QTc	Vibegron 200 mg	1 hour	5.0	(3.1, 6.9)

QTc	Vibegron 400 mg	1 hour	4.6	(2.7, 6.5)
QTc	Moxifloxacin 400 mg	2 hour	11.1	(9.2, 13.1)

Source: IRT through QT Consult (June 19, 2020 DARRTS) Table 1

The maximum mean increase in heart rate for the supratherapeutic dose of 400 mg was 12.4 bpm (90% CI: 10.7 – 14.1 bpm) at 3-hour postdose. The maximum increase in heart rate for the single 200 mg dose (which represents the steady state exposure at the therapeutic dose of vibegron 75mg) was less than 10 bpm. The increase in heart rate did not impact the overall IRT-QT conclusion for this QT study.

The IRT Consult team proposed the following label recommendations to section 12.2:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

According to the sponsor, (b) (4)

The (IRT-QT) reviewer does not agree (b) (4) *for the following reasons:*

(b) (4)

(b) (4) *(IRT-QT) propose to use labeling language which report the fold difference based on study dose. This language is consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.*

If the sponsor's estimate of therapeutic Cmax was found acceptable after review of the overall clinical pharmacology package, we would agree (b) (4) (b) (4) *and we recommend the following language:*

At an exposure 9X times the maximum concentration of the recommended daily dose (75 mg), vibegron does not prolong the QT interval to any clinically relevant

***Reviewer Comments:* We note the IRT-QT Consult team's conclusions of "no significant QTc prolongation effect of Vibegron was detected in this QT assessment " and we will consider the IRT-QT consulting team's labeling recommendation.**

8.4.10. Immunogenicity

Post marketing reports from Japan, the only country currently marketing vibegron, include reports of "rash". See 8.9 Safety in Postmarketing setting for additional discussion of these reports.

8.5. Analysis of Submission-Specific Safety Issues

The following sections include

- AEs of Clinical Interest (AECI)
- Adverse drug reactions (ADR)
- Events identified in the Kyorin postmarketing data from Japan.

8.5.1. AE of Clinical Interest (AECI)

Prespecified AECIs with accompanying rationale for selection are the following:

1. Potential MACCE and AEs of hypertension were evaluated due to a drug of the same class previously demonstrating increases in hypertension AE rates in clinical trials
2. AEs consistent with orthostatic hypotension were evaluated due to reports of decreases in blood pressure in healthy volunteer studies
3. AEs suggestive of cystitis or urinary tract infection were evaluated due to the potential for increases in PVR urine volume leading to urinary tract infection, given the vibegron mechanism of action
4. AEs suggestive of AST or ALT elevation were evaluated due to the potential for liver toxicity, as the drug is also metabolized in the liver

In the 12-week double-blind Studies 3003 and 301, AECI incidence of MACCE, hypertension, orthostatic hypotension, urinary tract infection, and ALT or AST elevation events was low across treatment groups and similar in the placebo and vibegron 75-mg groups. AECIs were reported in 7.7% of subjects receiving placebo, 8.1% of subjects receiving vibegron 75 mg, 12.1% of subjects receiving tolterodine, and 5.4% of subjects receiving vibegron 100 mg. The incidence of hypertension was 1.7% placebo; 2.2% vibegron 75-mg; 4.7% tolterodine, 1.1% vibegron 100 mg.

The following table summarizes AECIs in the 12-week double-blind studies 3003 and 301.

Table 58: AE of Clinical Interest in 12-Week Double-blind Studies 3003 and 301

	Placebo (N=909) n (%)	Vibegron 75mg (N=545) n (%)	Tolterodine ER 4 mg (N=430) n (%)	Vibegron 100 mg (N=369) n (%)
Any AE of Clinical Interest	70 (7.7)	44 (8.1)	52 (12.1)	20 (5.4)
Cystitis or Urinary Tract Infection	41 (4.5)	28 (5.1)	28 (6.5)	10 (2.7)
Urinary tract infection	33 (3.6)	27 (5.0)	25 (5.8)	0
Cystitis	4 (0.4)	1 (0.2)	1 (0.2)	8 (2.2)
Costovertebral angle tenderness	1 (0.1)	0	0	0
Dysuria	3 (0.3)	0	0	0
Escherichia urinary tract infection	0	0	1 (0.2)	0
Kidney infection	0	0	1 (0.2)	0
Pyelonephritis	0	0	0	1 (0.3)
White blood cells urine positive	1 (0.1)	0	0	1 (0.3)
Hypertension	15 (1.7)	12 (2.2)	20 (4.7)	4 (1.1)
Hypertension	10 (1.1)	9 (1.7)	11 (2.6)	1 (0.3)

Blood pressure increased	5 (0.6)	4 (0.7)	8 (1.9)	3 (0.8)
Blood pressure diastolic increased	0	0	1 (0.2)	0
Orthostatic hypotension	11 (1.2)	5 (0.9)	4 (0.9)	1 (0.3)
Dizziness	9 (1.0)	5 (0.9)	4 (0.9)	1 (0.3)
Syncope	2 (0.2)	0	1 (0.2)	0
MACCE	3 (0.3)	3 (0.6)	1 (0.2)	0
Cardiac failure congestive	0	1 (0.2)	0	0
Cerebrovascular accident	0	1 (0.2)	1 (0.2)	0
Vertebrobasilar insufficiency	0	1 (0.2)	0	0
Chest pain	3 (0.3)	0	0	0
Ejection fraction decreased	1 (0.1)	0	0	0
Elevated AST or ALT	5 (0.6)	2 (0.4)	3 (0.7)	5 (1.4)
Alanine aminotransferase	2 (0.2)	1 (0.2)	1 (0.2)	0
Aspartate aminotransferase	1 (0.1)	1 (0.2)	1 (0.2)	0
Transaminases increased	0	1 (0.2)	0	0
Blood bilirubin increased	1 (0.1)	0	1 (0.2)	0
Gamma-glutamyl transferase increased	1 (0.1)	0	0	2 (0.5)
Hepatic enzyme increased	1 (0.1)	0	1 (0.2)	0
Hepatic function abnormal	0	0	0	2 (0.5)
Liver function test abnormal	0	0	0	1 (0.3)

AE = adverse event; ER = extended release; ISS = integrated summary of safety; MACCE = major cardiac and cerebrovascular event
Notes: Adverse events are coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Source: ISS Table 2.26a with reviewer edits

For the long-term Studies 3004 and 302, and Merck Study 008, the overall incidence of AECIs (17.2% vibegron 75 mg, 20.3% tolterodine, 16.4% vibegron 100 mg, 16.8% vibegron 75 + 100 mg) was higher compared with the 12-week double-blind studies, which reflected the longer duration of data collection but the incidences were similar across treatment groups.

For the long-term studies, no clinically relevant differences were observed across treatment groups for the following AECIs:

- MACCE (0.7% vibegron 75 mg, 1.1% tolterodine, 1.7% vibegron 100 mg; 1.2% vibegron 75 + 100 mg)
- orthostatic hypotension (1.5% vibegron 75 mg, 3.2% tolterodine, 2.3% vibegron 100 mg, 1.9% vibegron 75 + 100 mg)

- cystitis or urinary tract infection (7.3% vibegron 75 mg, 11.9% tolterodine, 10.4% vibegron 100 mg, 8.9% vibegron 75 + 100 mg)
- ALT or AST elevation (1.1% vibegron 75 mg, 1.3% tolterodine, 0.3% vibegron 100 mg, 0.7% vibegron 75 + 100 mg).

For the remaining AECI hypertension, comparison of Study 3004 is appropriate as it had a balance of patients in the vibegron 75 mg and tolterodine groups treated for 52-weeks. In Study 3004, hypertension was the most commonly reported adverse event for both the vibegron and tolterodine groups (vibegron, 8.8%; tolterodine, 8.6%).

Reviewer Comments: ***The data demonstrated balance in all the prespecified AECIs in the studies for 12-weeks double-blind treatment and long-term up to 52-week treatment between vibegron and placebo groups. There are no concerns for the AECIs for vibegron 75mg, based on the reported AEs in these studies.***

8.5.2. Adverse Drug Reactions (ADRs)

Potential adverse drug reactions (ADRs) were identified from AE reports in Studies 3003 and its extension Study 3004 as well as serious and nonserious postmarketing reports from Kyorin in patients in Japan.

Study 3003:
ADRs in Study 3003 that met the numerical imbalance criterion (defined as ≥ 2% incidence in the vibegron 75 arm and ≥ 1% higher incidence in the vibegron 75 mg arm than in the placebo arm) were: headache, nasopharyngitis, diarrhea, nausea, and upper respiratory tract infection. The following table summarizes the ADRs from Study 3003.

Table 59: Adverse Drug Reactions ≥ 2% Vibegron 75mg Study 3003

	Placebo n (%)	Vibegron 75 mg n (%)
Number of Subjects	**540**	**545**
Headache	13 (2.4)	22 (4.0)
Nasopharyngitis	9 (1.7)	15 (2.8)
Diarrhea	6 (1.1)	12 (2.2)
Nausea	6 (1.1)	12 (2.2)
Upper respiratory tract infection	4 (0.7)	11 (2.0)

Source: Study 3003 CSR Table 14.3.1.14

Study 3004: Long-term Extension Study of 3003

Potential ADRs reported in ≥ 2% of subjects receiving vibegron 75 mg in Study 3004 that were not already listed as ADRs in Study 3003 were the following:

- hypertension (8.8% vibegron, 8.6% tolterodine)
- urinary tract infection (6.6% vibegron, 7.3% tolterodine)
- bronchitis (2.9% vibegron, 1.3% tolterodine)
- anemia (2.6% vibegron, 0.9% tolterodine)
- hyperglycemia (2.6% vibegron, 0.9% tolterodine)
- back pain (2.2% vibegron, 1.3% tolterodine)
- musculoskeletal pain (2.2% vibegron, 0.4% tolterodine)

Of the potential ADRs, the Sponsor eliminated hypertension, anemia, hyperglycemia, back pain, and musculoskeletal pain for reasons of lack of pharmacologic rationale or medical importance. The Sponsor proposed the following rationale for each elimination:

- Hypertension AEs
  - Balanced between the vibegron 75-mg and tolterodine treatment arms
  - Absence of a signal in Study 3003 and in the ABPM Study 1001
- Anemia
  - No temporal relationship between vibegron use and the anemia event
  - Pre-existing anemia or other confounding factors (e.g. Concomitant AEs of chronic gastritis, gastrointestinal tract bleeding, or pelvic fracture, which likely led to blood loss) with minimal decreases in red blood cell counts
  - Laboratory showed no clinically relevant changes in hemoglobin levels for pooled studies
  - Vibegron's mechanism of action is unlikely to affect the production or destruction of red blood cells
  - No clear pharmacological rationale for why vibegron would cause this event.
- Hyperglycemia
  - No temporal relationship between the initiation of vibegron and the onset of the hyperglycemia AE
  - Pre-existing diabetes mellitus or other confounding factors (eg, concomitant AEs of infection, hypothyroidism), and non-fasting laboratory specimens
  - No clear pharmacological rationale
- Back pain and musculoskeletal pain were eliminated as ADRs due to the
  - Lack of pharmacological rationale for relation to vibegron treatment

The remaining ADRs unique to Study 3004 were urinary tract infection and bronchitis which are summarized in the following table.

Table 60: Adverse Drug Reactions ≥ 2% Vibegron 75mg Unique to Study 3004

	Vibegron 75 mg n (%)	Tolterodine ER 4 mg n (%)
Number of Subjects	**273**	**232**
Urinary tract infection	18 (6.6)	17 (7.3)
Bronchitis	8 (2.9)	3 (1.3)

Up to 52 weeks of treatment includes up to 12 weeks of treatment in Study 3003
Source: Study 3004 CSR Table 14.3.1.14 with reviewer edits

<u>Reviewer Comments:</u> The Sponsor's identification of ADRs ≥ 2% AE rates from Studies 3003 and 3004 are reasonable and these ADRs should be reflected in labeling of these two studies.

8.5.3. Adverse Drug Reactions from Postmarketing Data

Japan is the only country with postmarketing data for vibegron.

Urinary Retention
Urinary retention has been reported in Japan with 11 serious and 44 nonserious events reported as of the data cutoff date for this submission, August 1, 2019. Urinary retention was also reported in Study 3003 in 2 subjects (0.4%) receiving placebo and 3 subjects (0.6%) receiving vibegron . In Study 3004, 3 subjects (1.1%) receiving vibegron in Study 3004 had urinary retention. The Sponsor reports that review of the clinical study data and postmarketing data showed that urinary retention was reported in subjects ≥ 60 years old and predominantly in subjects with bladder outlet obstruction.

Because of these urinary retention reports, the Sponsor proposes urinary retention be included as an ADR and also in the warning section of labeling.

<u>Reviewer Comments:</u> We agree with the Sponsor's proposal to include urinary retention in the ADRs and in the warning section of labeling.

8.6.Safety Analyses by Demographic Subgroups

Safety analyses were made for the following groups:

- Age < / ≥ 65 years old
- Age < / ≥ 75 years old
- Age > 75 years old
- Body Weight ≤ 25th Percentile
- eGFR ≤ 25th Percentile

- Pre-existing hypertension
- BPH
- Others including sex, diabetes mellitus, BMI, etc.

Age < / ≥ 65 years old

Across treatment groups, including the placebo group, the overall incidence of AEs was higher among subjects aged ≥ 65 years compared with subjects aged < 65 years in the pooled 12-week double-blind Studies 3003 and 301. In both age groups, the incidences of subjects reporting UTI, headache, dry mouth, URI, diarrhea and nausea AEs were higher for the vibegron 75-mg group compared with the placebo group. Similar percentages of subjects in the vibegron 75-mg group and the tolterodine group reported AEs, except for dry mouth where the tolterodine incidence rate exceeded the vibegron 75 mg incidence rate. Urinary tract infection and headache were the most frequently reported AEs in the vibegron 75-mg treatment group for both age groups. Other frequently reported AEs were similar in both age groups. The following table summarizes the 12-week double-blind AE's by subgroup.

Table 61: AEs in ≥ 2% Patients in 12-Week Double-blind Studies 3003 and 301 by Age < 65 Years and Age ≥ 65 Years

	Placebo n (%)	Vibegron 75 mg n (%)	Tolterodine ER 4 mg n (%)	Vibegron 100 mg n (%)
Subjects Aged < 65 Years	**N =550**	**N =299**	**N =259**	**N =239**
Any AE	144 (26.2)	101 (33.8)	93 (35.9)	65 (27.2)
Urinary tract infection	15 (2.7)	13 (4.3)	14 (5.4)	0
Headache	8 (1.5)	11 (3.7)	7 (2.7)	1 (0.4)
Nasopharyngitis	17 (3.1)	9 (3.0)	5 (1.9)	24 (10.0)
Nausea	3 (0.5)	7 (2.3)	4 (1.5)	0
Diarrhea	6 (1.1)	6 (2.0)	3 (1.2)	1 (0.4)
Hypertension	2 (0.4)	6 (2.0)	6 (2.3)	0
Subjects Aged ≥ 65 Years	**N =359**	**N =246**	**N =171**	**N=130**
Any AE	137 (38.2)	110 (44.7)	73 (42.7)	47 (36.2)
Urinary tract infection	18 (5.0)	14 (5.7)	11 (6.4)	0
Headache	5 (1.4)	11 (4.5)	4 (2.3)	0
Dry mouth	4 (1.1)	8 (3.3)	12 (7.0)	2 (1.5)
Upper respiratory tract infection	2 (0.6)	8 (3.3)	1 (0.6)	0
Diarrhea	4 (1.1)	6 (2.4)	6 (3.5)	1 (0.8)
Nasopharyngitis	19 (5.3)	6 (2.4)	6 (3.5)	11 (8.5)

Nausea	3 (0.8)	5 (2.0)	1 (0.6)	0

AE = adverse event; ER = extended release; ISS = integrated summary of safety
Adverse events are coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities coding dictionary version 21.1. Subject is counted only once in each preferred term.
NOTE: vibegron 100 mg was only studied in the Japan based study 301.
Source: ISS Table 2.29a with reviewer edits

<u>Reviewer Comments:</u> Higher incidences of AEs were seen in the older patient group in vibegron 75 mg compared to placebo with > 2% differences for headaches, dry mouth and upper respiratory tract infections.

Vibegron 100 mg data, all in Japanese patients from Study 301, is presented here for reference as there were unexpectedly few AEs reported in the vibegron 100 mg group in that study, possibly reflecting AE reporting differences in the Japanese study, e.g. headache, nausea, hypertension, urinary tract infection and upper respiratory tract infection etc. AEs all have 0% reporting in the vibegron 100 mg group compared to ≥ 2% in the vibegron 75mg group in Study 3004.

In pooled data from the long-term extension studies 3004 and 302 and Merck Study 008, for treatment up to 52 weeks, hypertension and urinary tract infection were the most frequently reported AEs in both subjects aged < 65 years and subjects aged ≥ 65 years. The following table summarizes the AEs reported in these studies.

Table 62: AE in ≥ 5% in Long-term Studies 3004, 302 and 008 by Age < 65 and Age ≥ 65

	Vibegron 75 mg n (%)	Tolterodine ER 4 mg n (%)	Vibegron 100 mg n (%)	Vibegron 75 and 100 mg n (%)
Subjects Aged < 65 Years	**N =144**	**N =293**	**N =209**	**N =353**
Any AE	79 (54.9)	179 (61.1)	135 (64.6)	214 (60.6)
Hypertension	10 (6.9)	13 (4.4)	2 (1.0)	12 (3.4)
Urinary tract infection	8 (5.6)	30 (10.2)	15 (7.2)	23 (6.5)
Subjects Aged ≥ 65 Years	**N =129**	**N =179**	**N =90**	**N =219**
Any AE	92 (71.3)	116 (64.8)	55 (61.1)	147 (67.1)
Hypertension	14 (10.9)	10 (5.6)	4 (4.4)	18 (8.2)
Urinary tract infection	10 (7.8)	21 (11.7)	10 (11.1)	20 (9.1)
Headache	9 (7.0)	9 (5.0)	2 (2.2)	11 (5.0)
Constipation	8 (6.2)	15 (8.4)	3 (3.3)	11 (5.0)
Diarrhea	8 (6.2)	8 (4.5)	5 (5.6)	13 (5.9)

AE = adverse event; ER = extended release; ISS = integrated summary of safety
Adverse events are coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities coding dictionary version 21.1. Subject is counted only once in each preferred term.
Source: ISS Table 2.29c with reviewer edits

Reviewer Comments: ***The most commonly reported AEs in both subgroups of < and ≥ 65 years were hypertension and UTIs. There was an imbalance of reports for hypertension in the older patient population with greater number of reports in the vibegron 75 mg subgroup compared to the tolterodine ER 4mg group. However, the ABPM study did not identify a vibegron BP signal.***

Caution should be used to interpret the data for the vibegron 100 mg dose in the Japanese extension study 302 due to unexpectedly low AE incidences.

Age ≥ 75th Percentile of the Pool
In the 12-week double-blind studies 3003 and 301, the 75th percentile for age was 69.0 years with the AE profile similar for patients aged ≥ 75th percentile compared with all other patients in the studies.

Body Weight ≤ 25th Percentile
The 25th percentile for body weight was 58.2 kg in the 12-week double-blind pooled studies 3003 and 301 and it was 65.3 kg for the long-term studies 3004, 302, and Merck Study 008 of up to 52-weeks vibegron treatment. No notable differences were observed in the AE profile for subjects with body weight ≤ 25th percentile compared with all other patients in the studies.

No notable differences were observed between the vibegron 75-mg group and the placebo group in the 12-week double-blind pooled studies for vital sign data.

Reviewer Comments: ***No notable differences were found in the analyses of the ≤ 25th Percentile weight subgroups. During review, the ClinPharm team investigated a lower weight class of < 10th percentile weight patients for possible vital sign changes. Another IRT-QT Cardiorenal consult was obtained to evaluate the data for any effect in that subgroup. The IRT-QT team did not identify any additional detrimental effect of 75 mg vibegron on the lowest weight classes. Refer to the ClinPharm review for additional information.***

Other Subgroups
Analyses of AE reports for other subgroups, including eGFR ≤ 25th Percentile, pre-existing hypertension, BPH, sex, diabetes mellitus at baseline and baseline BMI, did not show clinically relevant differences in AE reporting for vibegron in those subgroups.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No tumors or neoplasm inbalance were found in the ISS. Breast cancer was the only neoplasm reported in vibegron patients in the Merck Study 008 extension which is summarized in the following table:

Table 63: Neoplasm (Breast Cancer) Vibegron Studies in Study 008

	Number of Events Breast Cancer n (%)
Vibegron 50 mg	0
Vibegron 100 mg	1 (0.2)
Vibegron 50/ 100 mg	2 (0.3)
Tolterodine ER 4 mg	1 (0.4)
Source: Table 2.18f2 CSR-Study 008 and Table 2.18c ISS Reviewer generated table	

Reviewer Comments: ***Malignancy and neoplasm do not have increased events in the vibegron studies of up to 52-week duration.***

8.8.2. Human Reproduction and Pregnancy

No adequate and well-controlled clinical studies have been conducted in pregnant or lactating women. Three patients have become pregnant while participating in clinical studies as described below:

- In Study 008, 1 patient (receiving vibegron 100 mg + tolterodine) became pregnant during the extension study and discontinued from the study (Day 236). The pregnancy outcome was a healthy infant.
- In Study 3003, 1 patient (randomized to placebo) became pregnant between the End of Treatment Visit and the Follow-up Visit.
- In an ongoing IBS Study 2001, 1 subject had an ectopic pregnancy. The subject had a positive pregnancy test approximately 1 month after initiating study drug (baseline urine pregnancy test was negative). Study drug was discontinued, and treatment remains blinded. The pregnancy was terminated.

Reviewer Comments: ***There is no information on pregnancy with vibegron except for the one case where the patient discontinued from vibegron/ tolterodine treatment after pregnancy in Study 008 and delivered a healthy infant.***

8.8.3. Pediatrics and Assessment of Effects on Growth

There is no data on pediatric use of vibegron. OAB indication for this submission is for an adult patient population.

The Sponsor proposes pediatric studies for an indication of neurogenic detrusor overactivity (NDO) and proposes deferment of beginning pediatric studies until after sufficient safety and efficacy has been established in adults per the criteria set forth in section 505B(a)(3)(A)(ii) of the Pediatric Research Equity Act (PREA).

The Sponsor proposes studies in pediatric NDO age 3 to < 17 and has requested partial waiver of pediatric patients < 3 years of age as studies are impossible or highly impracticable in this youngest age group.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no experience with vibegron overdosage. Vibegron has been administered in clinical studies at single doses up to 600 mg (8 times the recommended therapeutic dose; Study 001) and multiple daily doses up to 400 mg/day for 14 days (> 5 times the recommended therapeutic dose; Study 002) with no serious adverse events reported. In case of suspected overdose, treatment should be symptomatic and supportive.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Vibegron has been approved in Japan for the treatment of adults with OAB since September 18, 2018, international birthdate (IBD). As of August 1, 2019 (data cutoff date for this submission), the cumulative, worldwide exposure to commercial vibegron was estimated to be 67,210 patient-treatment years, all in Japan. The calculation of patient-treatment years was based on distribution data received from Kyorin for the interval from the IBD to August 1, 2019 and the maximum daily dose of 50 mg.

From the Sponsor's 120-day submission update, a cumulative (IBD to March 20, 2019) summary of serious and nonserious events was tabulated using spontaneous reports from individual case safety reports, healthcare professionals, consumers, scientific literature, regulatory authorities and non-interventional studies. A total of 955 events have been reported in the postmarketing setting. Forty-nine of the reports were serious, and 906 of the reports were nonserious.

Among serious events, the most frequently affected SOC was Renal and Urinary Disorders (27 events), and the most frequently reported preferred term was urinary retention (24 events). All other serious events were reported from 1-3 times and consisted of the following: urinary tract

infection (3), pneumonia (2) , cerebral infarction (2), arrythmia, bile duct stone, cardiac failure, hepatic function abnormal, syncope, thalamus hemorrhage, hydronephrosis, hypoxia, pruritus, rash, white blood cell decrease, dysuria, renal failure, idiopathic interstitial pneumonia and implantable defibrillator insertion (1 each).

Among nonserious events, the most frequently affected SOCs were Gastrointestinal Disorders (221 events) and Renal and Urinary Disorders (210 events). Within the SOC of Gastrointestinal Disorders, the most frequently reported preferred terms (≥ 10 events reported) were constipation (75 events), dry mouth (47 events), diarrhea (21 events), and nausea (16 events). Within the SOC of Renal and Urinary Disorders, the most frequently reported preferred terms (≥ 10 events reported) were urinary retention (95 events), dysuria (65 events), and pollakiuria (17 events).

Across all PTs, urinary retention, constipation, and dysuria were the most frequently reported nonserious events. For nonserious skin disorders, the most frequently reported events were the following: pruritis (10 events), rash (9 events), drug eruption (8 events), eczema (8 events). For nonserious vascular disorders, hot flush was reported in 14 events.

The Sponsor proposes to include urinary retention and rash in labeling as ADRs for vibegron and to include a Warning in labeling for urinary retention.

Reviewer Comments: ***Urinary retention was reported in the postmarketing SAE and nonserious AE reports with the majority of SAE reports in men with a history of prostatic hyperplasia. However, 3 women were also reported with SAE of urinary retention. Agree with the Sponsor's proposal to include urinary retention as a Warning in labeling for both sexes, with note concerning additional risk in men with bladder outlet obstruction related to BPH.***

The post marketing reports include one SAE report of pruritis and one of rash but nonserious skin disorders included pruritis (10 events), rash (9 events), drug eruption (8 events), eczema (8 events), all of which may reflect skin disorders found in allergic-type reactions. Agree with the Sponsor's proposal to include rash as ADR in labeling but also consider including in labeling other possible reactions of pruritis, drug eruption, eczema.

Constipation was the second most commonly reported nonserious AE with 75 constipation events compared to 95 urinary retention events. Recommend including constipation as an ADR in labeling.

8.9.2. Expectations on Safety in the Postmarket Setting

Urinary retention, UTIs, constipation, and rash/ allergic-type skin reaction reports are to be expected in the prescribed patient population, based on the study AEs and postmarketing

reports, especially in the male population with pre-existing bladder outlet obstruction related to BPH. Urinary retention can be mitigated with standard-of-care treatment and agree with the Sponsor's proposal to include a Warning in labeling for urinary retention.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Vibegron has a consistent safety profile across data pools, similar to the findings in Study 3003 and 3004 with balanced findings between vibegron and placebo. There were no clinical meaningful differences found in the pooled studies which appeared to be dose related differences for 50, 75, or 100 mg exposures. Subgroup analyses for < 65 years and ≥ 65 years did not show major differences, relative to placebo in the groups but there were greater numbers of AEs seen in the older patient group in vibegron 75 mg compared to placebo with > 2% differences for headaches, dry mouth and upper respiratory tract infections.

Prespecified AEs of clinical interest, including select cardiovascular/vascular AEs, urinary tract/renal AEs, and other predefined AEs, were reported with relatively low frequency (~8% overall incidence in 12-week evaluations and ~17% overall incidence in 52-week evaluations) across treatment groups in all pools. There are no concerns for the AECIs for vibegron 75mg, based on the reported AEs in these studies.

BP and vital signs demonstrated no clinically significant BP changes in the ABPM study 1001 as noted in the ABPM IRT consult. Vital signs and cuff pressure measurements in Study 3003 and 3004 are consistent with the findings from the ABPM study.

There was no clinically relevant change from baseline in postvoid residual volume PVR urine volume at Week 12 for subjects treated with vibegron compared with placebo. From Study 3003, treatment with vibegron did not result in increased urinary retention in subjects. The mean (SD) changes from baseline at Week 12 were: placebo 2.1 (37.25) mL; vibegron 0.4 (38.27); tolterodine ER 3.1 (40.93). Assessments of PVR by subgroup (female vs male; men with BPH vs men without BPH) showed no increased risk for vibegron relative to placebo. PVR urine volume at baseline and at Week 12 by category (< 100 mL, ≥ 100 to < 200 mL, ≥ 200 to < 350 mL, and ≥ 350 mL) suggests no increased risk for PVR with vibegron relative to placebo in mean change from baseline at Week 12. With longer-term administration up to 52 weeks in Study 3004, there was no clinically relevant change from baseline in PVR urine volume on average for subjects treated with vibegron or with tolterodine ER. Few subjects reported an AE of "residual urine volume increased". Long-term treatment with vibegron did not demonstrate increased urinary retention in patients, both male and females in Study 3004, however the numbers of male patients were low.

Other safety laboratory analyses, ECGs, and QTc studies do not show clinically meaningful effects of vibegron on safety laboratory parameters (hematology, clinical chemistry, urinalysis, serum β-choriogonadotropin, and urine culture), ECGs, and QTc.

Post marketing experience in Japan, the only worldwide location where the drug has been marketed since September 2018, has identified urinary retention and rash/ allergic-type skin reaction as well as constipation which are recommended to be included in labeling.

9. Advisory Committee Meeting and Other External Consultations

No AC meeting was held for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling recommendations have been described in efficacy, section 6.1 and safety sections 8.9. See those sections for additional recommendations.

Labeling highlights will be noted below with reviewer comments in ***bold***:

Indication and Usage: Gemtesa ® is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

- ***The proposed indication is acceptable and the same as other beta-3 adrenergic agonist agents.***

Clinical Studies: The Sponsor proposes to include information on responder analyses for several endpoints, using response thresholds based on their anchor-based analysis of the Phase 2b Merck Study 008 data, as follows: ≥75% and 100% reduction in the average daily number of UUI episodes, % of patients with ≥50% reduction in the average daily urgency episodes, and Overactive Bladder Questionnaire Long Form (OAB-q LF) coping domain score.

- ***The Division of Clinical Outcomes Assessment (DCOA) conducted their own anchor-based analyses of Study 3003 data that suggests that clinical meaningful within-patient change thresholds for average daily number of UUI episodes and average daily number of "urgency" (need to urinate immediately) episodes are ≥ 90% reduction and ≥ 60% reduction, respectively. The format for presenting responder analyses in***

labeling for UUI and/or "urgency" episodes remains under discussion with particular interest shown for inserting a cumulative distribution function (CDF) graph for UUI only, instead of stating any specific responder thresholds. In addition, DCOA determined that the OAB-q LF coping domain lacked sufficient content validity (b) (4)

- ***All reference to "urgency" should be qualified as "urgency (need to urinate immediately)" as shown in the Study 3003 PVD term for patients*.**

10.2. Nonprescription Drug Labeling

Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended.

12. Postmarketing Requirements and Commitments

No PMR or PMC are recommended.

13. Appendices

13.1. References

Not applicable

13.2. Financial Disclosure

Vibegron development has been conducted by three separate Sponsors: Urovant, Merck, and Kyorin. Urovant has submitted the financial disclosure for all three Sponsors for Studies 3003, 3004 (Urovant), Study 008 (Merck), and Studies 301/ 302 (Kyorin).

Covered Clinical Study (Name and/or Number): Studies 3003/3004 (Urovant)
Study 008 (Merck)
Study 301/ 302 (Kyorin)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 823		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: (b) (6) site (b) (6): Study 008 (Merck) $36, 303.05 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: (b) (6) (b) (6) site (b) (6) (Merck) Study 008: 1500 Merck shares common stock (value at the time ~$60,000)		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 12		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Death Narratives

1. Subject (b) (6) in Study 3004

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	3a. WEIGHT	4-4b REACTION ONSET	5-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
UNKNOWN	UNITED STATES	Day / Month / (b) (6)	63 Years	Female	90.00 kg	Day / Month / Year (b) (6)	☒ PATIENT DIED Date (b) (6)

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [LOWER LEVEL TERM] (Related symptoms if any separated by commas)

Arteriosclerotic cardiovascular disease leading to death [Arteriosclerotic cardiovascular disease]

Case Description: Arteriosclerotic cardiovascular disease leading to death/Arteriosclerosis

This 63-year-old Caucasian female subject (b) (6) was participating in RVT-901-3004 and died on (b) (6)

The subject's medical history included overactive bladder, degenerative

(Continued on Additional Information Page)

☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
☐ LIFE THREATENING
☐ CONGENITAL ANOMALY
☐ OTHER

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (Include generic name)
#1) Blinded Study Drug (Vibegron) Tablet, 75 milligram
#2) Blinded Study Drug(Tolterodine ER placebo)Capsule

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 75 milligram, qd	#1) Oral
#2) UNK UNK, qd	#2) Oral

17. INDICATION(S) FOR USE
#1) Overactive bladder (Hypertonic bladder)
#2) Overactive bladder (Hypertonic bladder)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) (b) (6) Unknown	#1) Unknown
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
(b) (6) to Ongoing	Current Condition	Overactive bladder (Hypertonic bladder)
to Ongoing	Current Condition	Degenerative disc disease (Intervertebral disc degeneration)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Urovant Sciences GmbH
Viaduktstrasse 8
4051 Basel
SWITZERLAND

28. REMARKS
Patient ID: (b) (6)
Study ID: RVT-901-3004
Center ID: (b) (6)

24b. MFR CONTROL NO.
201812-URV-000283

25b. NAME AND ADDRESS OF REPORTER
(b) (6)

24c. DATE RECEIVED BY MANUFACTURER
23-JUL-2019

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
18-SEP-2019

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP: 4

7+13. DESCRIBE REACTION(S) continued

disc disease, vitamin D deficiency, myopia, presbyopia, and ampicillin allergy. No relevant concomitant medications were reported.

The subject received blinded study drug for overactive bladder in RVT-901-3003 study from (b) (6) and entered the long-term extension study. The subject received the first dose of blinded study drug in the extension RVT-901-3004 on (b) (6) days before the event.

On (b) (6) (visit 6), the subject was afebrile (36.7C). Vital signs included heart rate 69 beats/min, respiratory rate 16 breaths/min and an average blood pressure of 134/85 mmHg.

On (b) (6) (visit 7), the subject was afebrile (36.7C). Vital signs included heart rate 63 beats/min, respiratory rate 16 breaths/min and an average blood pressure of 131/74 mmHg.

On (b) (6) (visit 8), the subject was afebrile (36.3C). Vital signs included heart rate 63 beats/min, respiratory rate 15 breaths/min and an average blood pressure of 139/83 mmHg.

On (b) (6) the subject experienced arteriosclerotic cardiovascular disease leading to death and subsequently died at her residence. Additional associated comorbidities, signs, symptoms and clinical course of illness leading up to death were unknown.

On (b) (6) due to the subject having no next of kin, the site contacted the subject's emergency contact (neighbor) due to the subject not responding to previous phone calls/messages regarding the week 4 follow-up visit. At this time, the site was informed of the subject's passing.

On (b) (6) the site spoke with the coroner's office who confirmed no autopsy was performed. The death certificate was provided. The cause of death was reported as arteriosclerotic cardiovascular disease.

Study drug was continued and action taken with study medication was reported as dose not changed.

The event arteriosclerotic cardiovascular disease leading to death was considered fatal on (b) (6) The subject died on (b) (6) No autopsy was performed.

The investigator reported that arteriosclerotic cardiovascular disease leading to death was not related to investigational drug. Based on coroner report of death due to arteriosclerotic disease, prior history of hyperlipidemia, and no data in the investigational brochure (IB) or in the published literature linking vibegron to arteriosclerotic disease, it was determined by the Investigator that the event was not related to the product consumption

The sponsor has assessed the event arteriosclerotic cardiovascular disease leading to death as not related to investigational drug. The subject was noted to have normal vital signs and reported no adverse events throughout her lengthy study enrollment.

No additional information is expected.

Follow-up information received on 02-Feb-2019 and 13-Feb-2019
Death certificate was provided.

Follow-up information was received on 11-Jul-2019 and 17-Jul-2019:
The event term was updated from 'Death' to 'Arteriosclerotic cardiovascular disease leading to death'. Additional medical history was reported.

Follow up information received on 23-Jul-2019:
Action taken with the study drug updated from not applicable to dose not changed.

Subject was assigned to Vibegron.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	(b) (6)	Blood pressure measurement	134/85 mmHg	
2		Blood pressure measurement	131/74 mmHg	
3		Blood pressure measurement	139/83 mmHg	
4		Body temperature	36.7 °C	

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
5	(b) (6)	Body temperature	36.7 °C	
6		Body temperature	36.3 °C	
7		Electrocardiogram normal QRS Duration: 86 msec QT Duration: 407 msec PR Duration: 170 msec Evaluation: Normal	see note OTHER	
8		Heart rate beats/min	69 OTHER	
9		Heart rate beats/min	63 OTHER	
10		Heart rate beats/min	63 OTHER	
11		Respiratory rate breaths/min	16 OTHER	
12		Respiratory rate breaths/min	16 OTHER	
13		Respiratory rate breaths/min	15 OTHER	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
(b) (6) to Ongoing	Current Condition	Vitamin D deficiency (Vitamin D deficiency);
(b) (6) to Ongoing	Current Condition	Myopia (Myopia);
to Ongoing	Current Condition	Presbyopia (Presbyopia);
to Ongoing	Allergy Ampicillin allergy	Drug allergy (Drug hypersensitivity);

2. Subject [redacted] (Study 302) Kyorin Japan extension study

12.3.2 Descriptions of death, other serious adverse events, and some other important adverse events

12.3.2.1 Deaths

(1) Fall (Written case report: falling over), onset date: [redacted] (investigational drug administration day 29), seriousness: severe, severity: severe, medication status: terminated. Fall: Death, outcome date: [redacted] (1 day), causal relationship with investigational drugs: definitely none

Subject identification code: [redacted]
Administration group: Maintenance example of study drug dose
Gender: Female, Age: 69
Complications: osteoporosis, hypertension, insomnia, arthralgia
Concomitant medications: Bonaron tablet 5 mg, Eddie roll, Adfeed, Amlodipine OD, Zolpidem tartrate

Other adverse events: none

Continuance:

Acquired consent on [redacted] and started investigational drug administration at on [redacted]
On [redacted] of the same year, Visit 3 was scheduled but did not come to the hospital. On the same day, [redacted] the Clinical Research Coordinator (CRC) contacted the telephone, but there was no response. On the [redacted] of the same day, [redacted] the subject was dying at home. On [redacted] of the same month, [redacted] the cause of death was neck injury due to falls, the day of death was night of the [redacted] of the same month, and there was no other incidents. The following contents were heard about the behavior of the subject on the day of death. On the day of death ([redacted] of the same month), [redacted]

The outcome of this event was death.

Investigator's Investigation on Causal Relationship with Investigational Drug Opinion:

The cause of death was neck injury due to falls. On the day of the death, she drunk a considerable amount, and it is thought that the possibility of falls due to drunkenness is high, so the causal relationship with the investigational drug could be denied.

Sponsor's View on Causal Relationship with Investigational Drug:

We believe that the causal relationship with the investigational drug can be denied, as it is considered that the cause of the fall is extremely high due to considerable drinking.

13.4. Patient Voiding Diaries (PVD)

Study 008: Patient Voiding Diary

PRO Evidence Dossier NDA 213006

Figure 3: Sample Page from Patient Voiding Diary Used in the Phase 2b Clinical Trial (Study 008)

I started recording on this page when I got up for the day on:

Day of Week: ________________ Date: __ __/__ __/__ __

What time did you get up for the day? ___ ___ : ___ ___ AM ☐ PM ☐

If you check ACCIDENTAL URINE LEAKAGE, remember to check ONE of three boxes for REASON FOR LEAKAGE.

Time *(Please write in the time, and check a.m. or p.m.)*	Need to Urinate Immediately (Strong Urge) *(Check if you felt a strong urge or strong need to urinate immediately.)*	Urinated in Toilet	Accidental Urine Leakage *(Check if you had leakage of any amount.)*	Reason for Leakage *(If you had any leakage, please check the main reason.)*
__ __:__ __ AM ☐ PM ☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __:__ __ AM ☐ PM ☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __:__ __ AM ☐ PM ☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __:__ __ AM ☐ PM ☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __:__ __ AM ☐ PM ☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __:__ __ AM ☐ PM ☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __:__ __ AM ☐ PM ☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other

Continue recording on this page even if you wake up during the night or early morning. Start a new page tomorrow when you get up for the day.

What time did you go to bed for the night? ___ ___ : ___ ___ AM ☐ PM ☐

Did you record each time you urinated or leaked during this Diary Day? Yes ☐ No ☐

04/2005
US (English)

Restricted Confidential - Merck & Co., Inc., Whitehouse Station, New Jersey, USA Printed in USA

Study 3003: Patient Voiding Diary

Figure 4: Sample Pages from Patient Voiding Diary Used in Urovant Phase 3 Clinical Trials

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/

T D CHANG
12/09/2020 02:39:25 PM

MARK S HIRSCH
12/09/2020 03:43:22 PM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2020252
IND/NDA/BLA Number/ Referenced IND for NDA/BLA:	NDA 213006; Referenced IND for NDA:106410
Applicant:	Urovant Sciences GmbH
Established Name/Trade Name:	GEMTESA (vibegron) tablets
Indication:	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
Meeting Type/Deliverable:	Advice to Division
Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Clinical Reviewer	Debuene Chang
Clinical Team Leader (TL)	Mark Hirsch
Review Division Project Manager:	Nenita Crisostomo
COA Reviewer:	Parima Ghafoori
COA TL:	Selena Daniels
COA Acting Director:	Elektra Papadopoulos
Date Consult Request Received:	6/16/2020
Date COA Briefing Package/Submission Received:	12/26/2019
Date COA Review Completed:	10/9/2020

Please check all that apply: ☐ Rare Disease/Orphan Designation
☐ Pediatric

EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 213006 for vibegron. The proposed indication is for treatment of overactive bladder (OAB) in adult patients with symptoms of urge urinary incontinence, urgency, and urinary frequency.

The applicant used the following patient-reported outcome (PRO) instruments in their multicenter, international, randomized, double-blind, placebo-active (i.e., tolteradine)-controlled Phase 3 study (Study RVT-901-3003; hereon referred to as Study 3003) in adult patients (≥18 years) with OAB[1] (Table 1):

[1] OAB is defined as urgency, with or without urge urinary incontinence (UUI), usually associated with frequency and nocturia. d

Table 1. COAs Included in Study 3003

COA Name (COA Type)	Concept(s)	Endpoint Position[2]	Copy of COA
Patient Voiding Diary (PVD, PRO)	Urinary frequency (micturition)	Co-primary	Appendix A (paper copy)
	Urge urinary incontinence (UUI)	Co-primary	
	Urgency	Secondary	
Overactive Bladder Questionnaire long form (OAB-q LF)-Coping Domain (PRO)	Bother with impacts of OAB (coping behaviors)	Secondary	Appendix B

PRO= Patient-reported outcome

This submission included a COA evidence dossier. The Division seeks COA input on the adequacy of the PVD and OABq-Long Form (OABq-LF)-Coping domain (b) (4) (b) (4) (b) (4) The Division also seeks DCOA input on the thresholds for meaningful within-patient change on the relevant COA endpoints. While there were two Phase 3 trials, this review will focus on Study 3003 per the Division's request.

The review concludes the following:

PVD

The PVD was reviewed for content validity and other measurement properties, as well as the applicant's proposed thresholds for meaningful within-patient score change. The PVD has adequate measurement properties to support labeling claims as described below. However, there is uncertainty about the threshold that best represents a meaningful within-patient score change as the results from the phase 3 study (Study 3003) show a considerably higher threshold compared with the results obtained from the phase 2 study (Study 008)[3]; this has also been noted by the applicant.

- The PVD appears fit-for-purpose in the context of this particular drug development program to measure urinary frequency, UUI episodes, and urgency episodes. The applicant established content validity of this instrument in the target population through qualitative research (i.e., interviews and focus groups with OAB patients, interviews with clinicians), as well as the other measurement properties (construct validity, reliability, ability to detect change).
- To derive the thresholds for meaningful within-patient score change for each COA endpoint (urinary frequency, UUI, urgency), the applicant conducted anchor-based methods supplemented with empirical cumulative distribution function (eCDF) and probability density curves. As previously stated, the clinically meaningful within-patient

[2] Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.
[3] The PGI-Severity anchor scale was not administered in the Phase 2 trial; however, the PGI-Frequency was administered across both trials. Please see Section C8 of this COA review for list of anchors used in each study.

change threshold derived from Study 3003 was considerably higher compared with the threshold obtained from Study 008.

- For urinary frequency, a meaningful within-patient score change in average daily number of micturitions appears to fall somewhere in the range of -3.0 to -3.5 based on the anchor-based eCDF curves (using Patient Global Impression (PGI)-Severity anchor scale from Study 3003 data; patients deemed a 1-category change on the PGI-Severity anchor scale as a meaningful improvement) and -2.7 to -3.0 (using the PGI-Frequency anchor scale from Study 3003 data[4]). Based on Study 3003 data, when you look at the aforementioned ranges, there is minimal separation between the treatment and the placebo arm (see Appendix R).
- For UUI episodes, the applicant proposed a meaningful within-patient percent change of ≥75% reduction in average daily UUI episodes based on Study 008 data. However, based on Study 3003 data, a meaningful within-patient percent change threshold in average daily UUI episodes appears to be a ~ -90% reduction based on the anchor-based eCDF curves (using PGI-Severity anchor scale) and –a ~-89% reduction (using the PGI-Leakage anchor scale). Based on Study 3003 data, of the 382 patients treated with vibegron, 35.3% had ≥90% reduction in the average daily number of UUI episodes at 12 weeks compared to 23.7% of patients (n=371) receiving placebo.
- For urgency episodes, the applicant proposed a meaningful within-patient percent change of ≥50% reduction in average daily urgency episodes based on Study 008 data. However, based on Study 3003 data, a meaningful within-patient percent change threshold in average daily UUI episodes appears to be a ~ -61% reduction based on the anchor-based eCDF curves (using PGI-Severity anchor scale). Based on Study 3003 data, of the 492 patients treated with vibegron, 33.7% had ≥60% reduction in the average daily number of urgency episodes at 12 weeks compared to 28.1% of patients (n=474) receiving placebo.

- The PVD appears adequate to support labeling claims. Regarding labeling the concept of urgency, we recommend using the exact language of the concept measured [i.e., "urgency (need to urinate immediately)"] in the PVD.

OAB-q LF Coping domain

The OAB-q LF Coping domain was reviewed for content validity and other measurement properties. The applicant's proposed thresholds for meaningful within-patient score change were also reviewed. The submission did not include adequate documentation of content validity to support the OAB-q LF Coping domain (b) (4)

(b) (4)

[4] Based on Study 008, a meaningful within-patient score change in average daily number of micturitions appears to fall somewhere in the range of -2.3 to -2.5 based on the anchor-based eCDF curves using the PGI-Frequency anchor scale.

(b) (4)

[redacted]

Considerations for future medical product development in OAB:

For future clinical trials in this indication, in addition to the daily assessment of voiding symptoms, we recommend assessing other aspects of symptom burden, such as interference with activities of daily living to evaluate the effect of treatment on how a patient functions. While symptom (or behavior) bother may be an important clinical concept that is important to patients, it is only one aspect of symptom burden.

B. COMMENTS TO DIVISION

1. **Is the OABq-LF Coping domain reliable and fit-for-purpose?**

   DCOA Response:
   Refer to the Executive Summary related to the OAB-q LF Coping domain.

2. **Is the sponsor's proposal** (b) (4) **supported by the OABq-LF coping domain?**

   DCOA Response:
   Refer to the Executive Summary related to the OAB-q LF Coping domain.

3. **The sponsor proposes to include urgency episode data from Study 3003 as part of the main efficacy results in labeling. At the Pre-NDA meeting, COA staff recommended that electronic diaries be used to collect urgency episodes. Was the sponsor's method of data collection for urgency episodes adequate? For reference, the information is located at section 1.6.3 of the submission (i.e., FDA minutes-type C meeting PRO SAPTPP Jan 18, 2018, response Q1)**

   Reviewer's comment(s): *The applicant had originally planned to use an electronic version of the diary (eDiary) for the vibegron Phase 3 program; however, due to technical difficulties with the eDiary and the potential associated impact on data integrity, the applicant used the standard paper version of the diary in studies 3003 and -3004. Technical difficulties experienced by the eDiary vendor included glitches, freezes, and occasional screen blackouts (crashing) during which the device became inoperable in multiple rounds of User Acceptance Testing (UAT) and at a large investigator meeting.*

   Because eDiaries were not used in the Phase 3 trials, the applicant took additional steps to ensure high data quality, including a detailed plan for review, training, and monitoring of diaries. Training included how to access training videos for patients, review completed patient diaries with the patient, identify common diary errors and document any required corrections, and reinforce instructions for use.

   DCOA Response:
   While electronic data capture is generally recommended for daily diaries, data collection via use of paper is acceptable if proper procedures are implemented to ensure compliance and high data quality. It appears that the applicant took the appropriate measures to increase compliance and quality of data via the following:
   - Patients were provided calendars indicating when they were to complete the PVD at each visit to assist with diary completion compliance.
   - Study staff made reminder telephone calls to patients on Day 1 and Day 3 of every 7-Day PVD data collection period.
   - Patients could opt-in to receive SMS reminder messages on Day -1 and Day 6.

- Site staff were trained to review patient diaries page by page during study visits to check for inconsistencies, gaps in information, and ambiguous entries to be able to offer feedback and corrections in real time, when appropriate.

An information request (IR) was sent to the applicant on September 04, 2020 to provide details surrounding what type of corrections, if any, were made to the patient diaries by the investigative site staff and to confirm that patients' responses were not influenced by any investigative site staff. In response to the IR, the applicant confirmed that:

- Sites were instructed that only the patient can make corrections to the Patient Diary;
- Sites were trained that they must only repeat the definitions and instructions but not to interpret or paraphrase;
- In case of any missing response, the site would confirm that the patient intended to skip the item;
- Corrections must only be made by the patient if they can accurately recall the event.
- Corrections must be documented by the patient by drawing a horizontal line through the error, writing in the correct information, and writing their initial and the date of the correction.

However, we defer to the Statistical reviewer on whether the amount of missing data is within an acceptable range such that integrity of data is well maintained.

Question A:
In regard to the secondary endpoint "need to urinate immediately":

4. **Was appropriate concept elicitation conducted for the endpoint "need to urinate immediately"?**

DCOA Response:
It appears that the applicant utilized appropriate qualitative methods to elicit and characterize the concept of urgency (need to urinate immediately). According to the qualitative summary report for the patient interviews conducted in 2017, all participants (n= 11) noted that "need to urinate immediately" communicated the concept of "urgency (need to urinate immediately)". See Section C.6 of this review for more details on the content validity of the Patient Voiding Diary (PVD).

5. **Does the qualitative research results support the content validity, reliability and sensitivity to change for the endpoint "need to urinate immediately"?**

DCOA Response:
The PVD appears fit-for-purpose in the context of this particular drug development program to measure urgency (i.e., need to urinate immediately). The applicant established content validity of this instrument in the target population through qualitative research (i.e., interviews and focus groups with patients), as well as the other measurement properties (construct validity, reliability, ability to detect change).

6. **Are there notable differences in results between Study 008, where the "need to urinate immediately" heading in the PVD was qualified with "strong urge" versus Study 3003 where the "need to urinate immediately" heading in the PVD was not qualified but the patient instructions referred to "strong urge" for the "need to urinate immediately"?**

   DCOA Response:
   Reviewer's comment(s): *DCOA defers to the Statistical reviewer whether there are significant differences in results between Study 008 and Study 3003. From a COA perspective, it is difficult to directly compare the results from Study 008 and Study 3003 as different doses of the investigational treatment were used across the studies.*

7. **Does the qualitative research results support prior FDA advice to sponsor that the endpoint "need to urinate immediately" is reflective of, or equivalent to, urinary urgency for purpose of labeling claims?**

   DCOA Response: Refer to DCOA response to Question 4.

Question B:
In regard to the Patient Voiding Diary (PVD):

8. **Do the requested CDF figures that use the Phase 2b Study 008 patient Global Impression items as anchor scales aid in determining clinically meaningful improvement thresholds for the frequency of micturition endpoint?**

   DCOA Response*:*
   Refer to the Executive Summary related to the PVD.

9. **Did the sponsor clarify how they defined "stability" in micturition frequency scores and what magnitude of difference in scores was acceptable to define "stability"? Did the sponsor provide a rationale for why patients' scores across a three-week window from week 9 to week 12 adequately defines "stability"?**

   Reviewer's comment(s)*: Based on discussion with Clinical, a <=0.5 change in micturition is acceptable to define a stable patient in this study population.*

   DCOA Response*:*
   Yes. For the assessment of test-retest reliability, the analysis population was not defined using a patient global rating scale (e.g., patients that report the same global rating at two specified time points). Instead, the analysis population was defined by change in micturitions (i.e., <= 0.5 change in micturition) at Weeks 8 and 9 and Weeks 9 and 12. The applicant's rationale for selecting these timepoints was that these timepoints reflect a period in which patients were likely to be more stabilized on therapy, in a short enough duration where change would be expected to be minimal.

10. **Did the sponsor use anchor-based methods to look at mean changes in scores over time in subgroups of patients based on patients' severity status as an anchor? Did**

the sponsor evaluate the distribution of changes on the patient voiding diary (PVD) endpoints by changes on each anchor scale (e.g., using the patient Global Impression items) and by providing descriptive statistics for improvement in PVD scores for each level of categorical improvement in the anchors by patients' severity status (e.g., using N [total number, mean, median, standard deviation, range, and confidence intervals])?

DCOA Response*:*
Yes. The applicant included data on the mean change and percent change in PVD endpoints at Week 8 by category of change in anchor scales for Study 008 (See Table 8 in PRO evidence dossier).

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Regulatory Background:

- There has been several communications with the applicant regarding the adequacy of the clinical outcome assessments (COAs), which included advice on the following:
  - Refine definition of urgency (i.e., changing [redacted] (b) (4) to "need to urinate immediately")
  - Refine definition of urgent nighttime voids associated with overactive bladder (OAB)
  - Improve Patient Voiding Diary (PVD) to discourage retrospective recording beyond memory capabilities for valid logging of nighttime voids.
  - Confirm content relevance of PVD via cognitive interviews
  - Compilation of qualitative and quantitative evidence to document reliability and validity of the COAs

Reviewer's comment(s): *In 2007 (meeting minutes issues March 22nd, 2007), the Agency acknowledged that the qualitative research confirms that inability to defer urination (i.e., "need to urinate immediately") is clinically important to patients with OAB. However, the Agency recommended changing* [redacted] (b) (4) *to "need to urinate immediately" (i.e., the Agency did not agree with applicant's proposed verbiage, and required demonstration of discriminant validity). Following Agency's advice, the applicant changed the column heading in the PVD to "need to urinate immediately (strong urge)". All subsequent PVD versions remained consistent. However, for the Phase 3 trials, the applicant had stated that "need to urinate immediately" without the parenthetic would be used based on completed patient interviews in 2017.*

Previous COA Reviews:

- C2018232_IND 106410_Kovacs dated 09/13/2018 (DARRTS Reference ID: 4320244)
- C2018187_IND 106410_Kovacs dated 08/08/2018 (DARRTS Reference ID: 4303761)
- C2018056_IND 106410_Kovacs dated 08/08/2018 (DARRTS Reference ID: 4303826)
- C2017307_IND 106410_Kovacs dated 06/08/2018 (DARRTS Reference ID: 4250875)
- C2017133_ IND 106410_Kovacs dated 01/03/2018 (DARRTS Reference ID: 4202794)

- AT 2011-055 _IND 106410_ Stansbury dated 07/07/2011 (DARRTS Reference ID: 2970611)

Disease Background:
Per the applicant, "the International Continence Society (ICS) defines OAB as urgency, with or without urge incontinence, usually associated with frequency and nocturia. Urgency is defined as a sudden compelling desire to void which is difficult to defer. Urge urinary incontinence (UUI) is the involuntary loss of urine accompanied by urgency (referred to as OAB Wet) and is present in approximately one-third of patients with OAB. In the absence of incontinence, OAB is referred to as OAB Dry. UUI is distinguished from stress urinary incontinence, which is the involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing. When both components are present, the classification is mixed urinary incontinence and the Investigator will make a determination of either urgency or stress specified as the predominant component."

Investigational Product:
Per the applicant, "Vibegron is a potent, highly selective, human beta-3 adrenergic receptor (AR) agonist, with a half maximal effective concentration (EC50) of 1.1 nM (84% receptor activation) in buffer and 1.7 nM (102% receptor activation) in the presence of 40% human serum. Vibegron demonstrated negligible intrinsic activity for cloned human beta-1 AR and did not bind to beta-1 AR."

Other materials reviewed:
- Clinical study report (i.e., "An International Phase 3, Randomized, Double-Blind, Placebo- and Active (Tolterodine)- Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder_
- Statistical analysis plan for Study RVT-901-3003
- Meeting minutes dated February 12th, 2018 (DARRTS Reference ID: 4219995)

2 CONTEXT OF USE

2.1 Clinical Trial Population

The target population for Study RVT-901-3003 are adults (≥ 18 years) who have a history of OAB[5] (as diagnosed by a physician) for at least 3 months prior to the Screening Visit and meets either the OAB Wet or OAB Dry criteria[6] (described in Clinical Study Protocol RVT-901-3003 (15 Nov 2018)).

A complete list of the inclusion and exclusion criteria is summarized in Clinical Study Protocol RVT-901-3003 (15 Nov 2018).

[5] OAB is defined as urgency, with or without urge urinary incontinence (UUI), usually associated with frequency and nocturia. Urodynamic evaluation is not required.
[6] Based on the Patient Voiding Diary returned both at the Run-in Visit and Baseline Visit (all Complete Diary Days must be used in determining eligibility).

2.2 Clinical Trial Design

Table 2 describes the clinical trial design of Study RVT-901-3003.

Table 2. Clinical Trial Design for Study RVT-901-3003

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☒ Active comparator-controlled ☐ Cross-over ☒ Multinational ☐ Non-inferiority	12 weeks	Yes

Refer to the clinical study protocol for more details on the clinical trial design.

Reviewer's comment(s): *The Phase 3 program consisted of two studies to support registration: efficacy and safety study, RVT-901-3003 & safety study RVT-901-3004. Approximately 1,400 men and women with overactive bladder were enrolled at approximately 330 study sites.*

- *Patients who met all eligibility criteria were randomized 5:5:4 to receive either vibegron 75 mg, placebo, or tolterodine ER 4 mg in a double-blind fashion. Between the Baseline and Week 12 Visits, patients attended Visits at Weeks 4 and 8.*
- *Study RVT-901-3003 consisted of a Screening Period (1 to 5 weeks), a single-blind Run-in Period (2 weeks), a randomized double-blind Treatment Period (12 weeks), and a Safety Follow-up Period (4 weeks).*
- *Patients who completed 12-weeks of treatment in RVT-901-3003; may have been offered the opportunity to enroll in a 40-week double-blind extension study RVT-901-3004 to evaluate the long-term safety and efficacy of vibegron 75 mg in patients with OAB.*
- *Subjects who had been randomized to either active treatment group in RVT-901-3003 continued that same active treatment in RVT-901-3004 and subjects who had been randomized to the placebo group in RVT-901-3003 were randomized to receive vibegron or tolterodine in RVT-901-3004.*

According to the PRO evidence dossier, culturally appropriate versions of the paper diary was created in more than 50 languages for prior trials to Phase 3 study. The process involved the following:

- *Two independent forward translations by speakers native to the target country ad fluent in English*
- *Comparison and reconciliation of the translation*
- *Back-translation by a native English speaker*
- *Comparison of source and backward version*
- *Pre-testing for comprehension in a small study sample of the target population*

Per the applicant, for any additional language requirement for Phase 3, a similar process was followed, and no significant issues were found.

2.3 Endpoint Position, Definition, and Assessment Schedule

Table 3 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study RVT-901-3003. Note that this table includes the primary endpoints and the endpoints related to the Division's questions in the consult request. Refer to the clinical study protocol for the complete list of endpoints.

Table 3. Endpoint Position, Definition, and Assessment Schedule for Study RVT-901-3003:

Endpoint Position	**Assessment (If COA, specify Name and Type)**	**Endpoint Definition**	**Assessment Frequency**
Co-primary	Patient Voiding Diary (PVD, PRO)	Change from baseline at week 12 in average number of micturitions per 24 hours in all OAB patients	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: 7 diary days prior to clinic visit (Screening, Baseline, Weeks 2, 4, 8, and 12)**
	PVD (PRO)	Change from baseline at week 12 in average number of UUI episodes per 24 hours in OAB Wet patients	
Secondary ☒ Multiplicity adjusted	PVD (PRO)	Change from baseline at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB subjects	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: 7 diary days prior to clinic visit (Screening, Baseline, Weeks 2, 4, 8, and 12)**
Secondary ☒ Multiplicity adjusted	Overactive Bladder Questionnaire long form (OAB-q LF)-Coping Domain (PRO)	Change from baseline at Week 12 in Coping Domain score in all OAB subjects	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Baseline, Week 12** ☐ Assessment at cross-over or early discontinuation

PRO= Patient-reported outcome

Reviewer's comment(s):
In regard to the statistical analyses, the applicant used an overall testing strategy using a stepwise gate-keeping procedure to control the overall Type-I error rate at α=0.05 level. Each of

the concepts are scored independently and analyzed as a separate endpoint in the statistical analyses

The PVD was administered serially for seven days prior to the clinic visit. In regard to mode of administration, the applicant had originally planned to migrate the PVD to an eDiary platform. However, due to number of technical difficulties (i.e., glitches, freezes, occasional screen blackouts (crashing)) which, in some instances, had caused loss of data or duplication of data in the database, the applicant reverted back to use of the standard paper version of the diary in registrational studies, RVT-901-3003 and RVT-901-3004. Therefore, all enrolled patients in the Phase 3 trials, as well as all previous trials, used the paper version of PVD. It is important to note that prior efforts in development and analysis of measurement properties of PVD were also conducted using the paper-based version.

According to the applicant, the following measures were established to increase the compliance and maintain the integrity of the data in the Phase 3 trials:

- *Training patients on diaries and diary completion;*
- *Reviewing completed diaries with patients during clinic visits to mitigate diary completion errors;*
- *Making phone calls and utilizing the SMS text messaging system to remind patients about aspects of diary completion;*
- *Providing patients with study tools for reference and to ensure compliance;*
- *Developing the Handbook for Patient Diary and Urinary Volume Collection (UVC) and the patient practice page;*
- *Providing resources available on the study portal including the patient training videos.*

An information request (IR) was sent to the applicant on September 04, 2020 to provide details surrounding what type of corrections if any, were made to the patient diaries by the investigative site staff and to confirm that patients' responses were not influenced by any investigative site staff. In response to the IR, the applicant confirmed that:

- *Sites were instructed that only the patient can make corrections to the Patient Diary;*
- *Sites were trained that they must only repeat the definitions and instructions but not to interpret or paraphrase;*
- *In case of any missing response, the site would confirm that the patient intended to skip the item;*
- *Corrections must only be made by the patient if they can accurately recall the event. Corrections must be documented by the patient by drawing a horizontal line through the error, writing in the correct information, and writing their initial and the date of the correction.*

While electronic data capture is generally recommended for daily diaries, data collection via use of paper is acceptable if proper procedures are implemented to ensure compliance and high data quality. However, this reviewer defers to the Biostatistics reviewer whether the amount of missing data is within an acceptable range such that integrity of data is well maintained.

2.4 Labeling or promotional claim(s) based on the COA

The applicant proposed the following specific targeted COA-related labeling claims (*blue font*) for GEMTESA.

(b) (4)

Table 1: Mean Baseline and Change from Baseline at Week 12 Micturition Frequency, Urge Urinary Incontinence, (b) (4) and Volume Voided per Micturition

Parameter	***Placebo***	***GEMTESA 75 mg***
Average Daily Number of Micturitions		
Baseline mean (n)	*11.75 (520)*	*11.31 (526)*
Change from Baseline" (n)	*-1.3 (475)*	*-1.8 (492)*
Difference from Placebo	*-0.5*	
95% Confidence Interval	*-0.8 to -0.2*	
p-value	*<0.001*	
Average Daily Number of UUI Episodes		
Baseline mean (n)	*3.49 (405)*	*3.43 (403)*
Change from Baseline" (n)	*-1.4 (372)*	*-2.0 (383)*
Difference from Placebo	*-0.6*	
95% Confidence Interval	*-0.9 to -0.3*	
p-value	*<0.0001*	
Average Daily Number of (b) (4)		
Baseline mean (n)	*8.13 (520)*	*8.11 (526)*
Change from Baseline" (n)	*-2.0 (475)*	*-2.7 (383)*
Difference from Placebo	*-0.7*	
95% Confidence Interval	*-1.1 to -0.2*	
p-value	*0.0020*	

(b) (4)

Average Volume Voided (mL) per Micturition		
Baseline mean (n)	*148.3 (514)*	*155.4 (524)*
Change from Baseline" (n)	*2.2 (478)*	*23.5 (490)*
Difference from Placebo	*21.2*	
95% Confidence Interval	*14.3 to 28.1*	
p-value	*<0.0001*	

" Least squares mean adjusted for treatment, baseline, sex, geographical region, study visit, and study

visit by treatment interaction term

(b) (4)

Reviewer's comment(s):
The vibegron study showed statistically significant differences in the primary and secondary endpoints (i.e., number of daily micturitions, number of daily UUI episodes and number of daily urgency episodes at week 12), as measured by PVD:

- *For micturitions, mean change from baseline is approximately -1.8 for the vibegron, and - 1.55 for tolterodine, and – 1.3 for placebo*
- *For UUI, mean change from baseline is approximately -2.0 for the vibegron, and - 1.75 for tolterodine, and – 1.4 for placebo*
- *For urgency episodes, mean change from baseline is -2.7 for the vibegron, -2.45 for tolterodine, and – 2.0 for placebo*

However, the between-group differences are very small, as such it is important to look at within-patient change. Refer to Section C.8 of this review for score interpretability and discussion on whether the observed improvements in the COAs are meaningful.

From this reviewer's perspective, the PVD appears adequate to support labeling claims. Regarding labeling the concept of urgency, we recommend using the exact language of the concept measured [i.e., "urgency (need to urinate immediately)"] in the PVD. (b) (4) *Refer to Sections C.6, C.7, and C.8 for more details regarding the adequacy and/or inadequacy of these instruments.*

3 CONCEPTUAL FRAMEWORK

The conceptual framework(s) for PVD[7] and OAB-q-LF-Coping domain are shown in Tables 4 and 5, respectively.

Table 4. Conceptual Framework for PVD

(b) (4)

Table 5. Conceptual Framework for OAB-q-LF-Coping domain

(b) (4)

Reviewer's comment(s):
The conceptual frameworks provided in the PRO evidence dossier were not structured in the proper format. This reviewer generated the frameworks shown above.

4 CLINICAL OUTCOME ASSESSMENT(S)

Patient Voiding Diary (PVD)

The PVD is a patient-reported daily diary (log form) is designed to record the patient's daily urinary output, as well as the following OAB-specific symptoms:

- Urinary frequency
- Incontinent episodes (accidental urine leakage)
- Urinary urgency (need to urinate immediately)

Each item is completed as the event occurs during the seven days prior to the clinic visit. For each void, the patient indicates by checking a box whether they:

- Felt the need to urinate immediately (felt a strong urge to urinate) just before urination
- Urinated in the toilet
- Leaked urine of any amount

[7] Note the conceptual framework for the PVD is for the concepts related to the Division's questions in the consult request.

Overactive Bladder Questionnaire long form (OAB-q LF) Coping domain

(b) (4)

5 SCORING ALGORITHM

PVD

Each event for micturitions, UUI, and urgency episodes is counted as a discrete variable.

The PVD was used to calculate the study endpoints as follows:

- ***Micturitions:*** *Change from baseline, where average daily micturitions is defined as the total number of voids for all complete diary days divided by the number of complete diary days during the diary collection period*

- ***UUI episodes:*** *Change from baseline, where average daily UUI episodes is defined as the total number of UUI episodes (main reason for accidental urine leakage marked as urge) for all complete diary days, divided by the number of complete days during the diary collection period.*

- ***Urgency episodes:*** *Change from baseline, where average daily urgency episodes is defined as the total number of urgency episodes for all complete diary days, divided by the number of complete days during the diary collection period*

(b) (4)

OAB-q LF Coping domain

(b) (4)

6 CONTENT VALIDITY

PVD

An overview of the development activities for the PVD is shown in Table 6.

Table 6. Qualitative Sources of Evidence for Content Validity and Comprehension of PVD

Patient Input	Date	Number of OAB Patients
Pre-test of PVD prior to a pilot probe study Note: This draft diary was based on prior trial diaries, KOLs, and on literature in which patient input was solicited in developing PRO measures. Note that this preceded the FDA Draft PRO Guidance by 7 years.	March 1999[a]	20
Focus groups of pilot probe study with tolterodine	July 1999[a]	13
Comprehension testing of instructions	August 1999[a]	6
Focus groups of Epidemiology Endpoint Assessment Study 014 [Brown, 2003] participants	July 2000[a]	8
Patient interviews – open-ended concept elicitation without having seen diary, followed by cognitive debriefing of PVD and other PRO measures	October 2006[a]	11
Patient interviews, initially open-ended, then probing changes in diary endpoints that would be considered meaningful	August 2017[b]	11

PVD: Patient Voiding Diary; KOL: Key opinion leader; PRO: Patient-reported outcome
[a] See information in Type C Meeting Request from Jan 2018 (Appendix 3)
[b] Patient interviews were conducted August 2017; Patient Interview Report from September 2017 (Appendix 8)

(retrieved from Table 4 of the PRO evidence dossier)

The findings of the qualitative research are summarized as follows:

- Based on hybrid concept elicitation and cognitive interviews (n=11) conducted in October 2006, most patients spontaneously mentioned the following three key symptoms: high frequency of urination, urinary urgency, and leakage (see Type C Meeting Background Package from 05 January 2007 for more information). When referring to urinary urgency, most participants spontaneously used the phrases 'a strong urge', 'a sudden urge', 'an urgent urge'. All patients interviewed indicated that the strength of the urge to urinate was determined by the amount of time they had to get to the bathroom to avoid leakage with a sense of urgency indicating that they had very little time (i.e., 'gotta go now' or needing to urinate immediately). In addition, 9 out of 11 participants, preferred the addition of "immediately" to the column heading. Therefore, the applicant recommended revising the heading to "Strong Urge to Urinate Immediately".

- During the hybrid concept elicitation and cognitive interviews (n=11) conducted in August 2017, all (11/11) or nearly all (10/11) participants endorsed OAB symptoms of frequent urination, urinary urgency and leakage. Among the 10 participants who reported leakage, nine indicated they were always able to identify the cause unless they were unaware of the leakage at the time it happened. All 10 participants with leakage stated that they could easily identify episodes they would classify as urge-related: leakage that occurred as they

were rushing to or were unable to make it to the bathroom in time. In addition, nine of these participants said they could always differentiate urge-related episodes from all others. These results suggest that patients can accurately classify their leakage within the diary for computation of the frequency of UUI episodes.

- Clinicians provided input on the content of the diary, how the symptoms were collected, and plans for PVD implementation.

Reviewer's comment(s):
This reviewer believes that the qualitative data supports the relevance, meaningfulness, and coverage of symptoms in the diary, as well as the importance of such symptoms to patients.

For additional information, please refer to DCOA's previous review on this application (i.e., C2017307_IND 106410_Kovacs dated 01/08/2018 (DARRTS Reference ID: 4250875)

OAB-q LF Coping domain

(b) (4)

Reviewer's comment(s): (b) (4)

(b) (4)

(b) (4)

7 OTHER MEASUREMENT PROPERTIES

PVD

The measurement properties of the PVD have been evaluated in multiple clinical trials, a separate observational Endpoint Assessment Study (EAS) [Brown, 2003], a prior Phase 2b trial of MK-869, and a Phase 2b trial of compound MK-634, which was subsequently discontinued. More recently, the PVD was used in Study 008. A summary of the findings from prior studies and Study 008 is shown in Table 7.

Reviewer's comment(s): *In general, the other measurement properties for the PVD (i.e., reliability, construct validity, ability to detect change) were reasonable and fell within acceptable ranges.*

For the assessment of test-retest reliability, the analysis population was not defined using a patient global rating scale (e.g., patients that report the same global rating at two specified time points). Instead, the analysis population was defined by change in micturitions (i.e., <= 0.5 change in micturition) at Weeks 8 and 9 and Weeks 9 and 12. The applicant's rationale for selecting these timepoints was that these timepoints reflect a period in which patients were likely to be more stabilized on therapy, in a short enough duration where change would be expected to be minimal. Identical test-retest reliability results (i.e., ICC (95% CI)= 0.86 (0.82,0.89)) were found in patients from week 8 to 9 and from week 9 to 12. Based on discussion with Clinical, <=0.5 change in micturition is considered appropriate to define a stable patient in this study population.

Table 7. Summary of Psychometric Properties of PVD from Prior Studies and Study 008

Measurement Property	Micturitions	Urge Urinary Incontinence (UUI) Episodes	Urgency Episodes
Test-retest reliability, estimate (95% CI)[a]	EAS 014: (n=144) ICC=0.82 (0.76, 0.87)	EAS 014: (n=144) ICC=0.81 (0.74, 0.86)	EAS 014: (n=144) ICC=0.86 (0.82, 0.90)
	Study 008: Weeks 8 to 9 (n=213) ICC=0.86 (0.82, 0.89)	Study 008: Weeks 8 to 9 (n=161): ICC=0.96 (0.95, 0.97)	Study 008: Weeks 8 to 9: (n=213) ICC=0.93 (0.91, 0.95)
	Study 008: Weeks 9 to 12 (n=200) ICC=0.86 (0.82, 0.89)	Study 008: Weeks 9 to 12 (n=152): ICC=0.96 (0.95, 0.97)	Study 008: Weeks 9 to 12 (n=200) ICC=0.92 (0.90, 0.94)
Construct (convergent) validity	EAS 014: Associated with urgency (r=0.40) and UUI (r=0.20)	EAS 014: Associated with urgency (r=0.39), micturitions (r=0.19)	EAS 014: Associated with UUI (r=0.43) and micturitions (r=0.40)
	MK-634 Study 007: Association analyses of CFB measures supported relationships in direction and of magnitude expected (r=0.3 to 0.54 with other diary endpoints; 0.25 to 0.38 with patient global impression of change)	MK-634 Study 007: Association analyses of CFB measures supported relationships in direction and of magnitude expected (r=0.3 to 0.42 with other diary endpoints; 0.19 to 0.27 with patient global impression of change)	MK-634 Study 007: Association analyses of CFB measures supported relationships in direction and of magnitude expected (r=0.28 to 0.56 with other diary endpoints, 0.27 to 0.35 with patient global impression of change)
	Study 008: Association analyses of CFB measures supported relationships in direction and of magnitude expected (r= 0.43 to 0.54 with other diary endpoints; 0.25 to 0.33 with patient global impression of change)	Study 008: Association analyses of CFB measures supported relationships in direction and of magnitude expected (r= 0.43 to 0.55 with other diary endpoints; 0.22 to 0.32 with patient global impression of change)	Study 008: Association analyses of CFB measures supported relationships in direction and of magnitude expected (r= 0.54 to 0.55 with other diary endpoints; 0.30 to 0.34 with patient global impression of change)

Measurement Property	Micturitions	Urge Urinary Incontinence (UUI) Episodes	Urgency Episodes
Responsiveness to change, Week 8 placebo-adjusted mean (95% CI)	MK-634 Study 007: Statistically significant differences in CFB in number of micturitions for both doses of MK-634 vs placebo MK-634 50 mg: -0.86 (-1.33, -0.39) MK-634 125 mg: -1.14 (-1.62, -0.66) MK-634 375 mg: -1.20 (-1.68, -0.73)	MK-634 Study 007: Statistically significant differences in CFB in number of UUI episodes for both doses of MK-634 vs placebo MK-634 50 mg: -0.29 (-0.67, 0.09) MK-634 125 mg: -0.42 (-0.81, -0.04) MK-634 375 mg: -0.71 (-1.09, -0.33)	MK-634 Study 007: Statistically significant differences in CFB in number of urgency episodes for both doses of MK-634 vs placebo MK-634 50 mg: -1.07 (-1.79, -0.35) MK-634 125 mg: -1.46 (-2.17, -0.74) MK-634 375 mg: -1.52 (-2.23, -0.81)
	MK-869 Study 011: Non-significant differences in CFB in number of daily micturitions for all doses MK-869 vs placebo, but significant changes for tolterodine 2 mg MK-869 2 mg (% change): -1.6% (-6.7%, 3.5%) Tolterodine 2 mg (% change) -6.4% (-11.4%, -1.3%)	MK-869 Study 011: Non-significant differences in CFB in number of daily UUI episodes for all doses MK-869 vs placebo, but significant changes for tolterodine 2 mg MK-869 2 mg (% change): -7.5% (-21.5%, 6.5%) Tolterodine 2 mg (% change) -23.4% (-37.4%, -9.3%)	MK-869 Study 011: Non-significant differences in CFB in number of daily urgency episodes for all doses MK-869 vs placebo, but significant changes for tolterodine 2 mg MK-869 2 mg (% change): -6.4% (-20.3%, 7.4%) Tolterodine 2 mg (% change) -17.3% (-31.1%, -3.5%)
	Study 008: Vibegron 50 mg: -0.64 (-1.11, -0.18) Vibegron 100 mg: -0.91 (-1.37, -0.44)	Study 008: Vibegron 50 mg: -0.72 (-1.11, -0.33) Vibegron 100 mg: -0.71 (-1.10, -0.32)	Study 008: Vibegron 50 mg: -0.76 (-1.43, -0.10) Vibegron 100 mg: -1.24 (-1.90, -0.58)

Source: Table 2-5 of Appendix 1 of Type C Meeting Request from 18 January 2018 Guidance Meeting for PRO Dossier (Appendix 3)
EAS: Endpoint Assessment Study; UUI: urge urinary incontinence; ICC: intraclass correlation coefficient; CI: confidence interval
[a] Minimum acceptable reliability estimates for measures being used for research purposes are ≥ 0.70.

(retrieved from Table 5 of the PRO evidence dossier)

OAB-q LF Coping domain

(b) (4)

(b) (4)

Reviewer's comment(s): (b) (4)

(b) (4)

(b) (4)

8 INTERPRETATION OF SCORES

PVD

The following responder definitions were used for the PVD-related endpoints:

- **UUI episodes**: ≥75% reduction in number of daily UUI episodes
- **Urgency episodes**: ≥50% reduction in number of daily urgency episodes
- **Micturitions**: No responder definition proposed for this concept

The applicant conducted anchor-based analyses using both data from Study 008 and 3003.

For Study 008, the following anchors were used:

- Patient Global Impression of Symptom Frequency (PGI-Frequency)
- Patient Global Impression of Urgency-related Leakage (PGI-Leakage)
- Patient Global Impression of Control (PGI-Control)

For Study 3003, the following anchors were used:

- Patient Global Impression of Symptom Frequency (PGI-Frequency)
- Patient Global Impression of Severity (PGI-Severity)
- Patient Global Impression of Urgency-related Leakage (PGI-Leakage)
- Patient Global Impression of Control (PGI-Control)

Reviewer's comment(s):
Regarding the adequacy of the anchor scales, this reviewer believes the following:

- *PGI-Severity and PGI-Frequency are appropriate anchor scales for the concept of urinary frequency (micturitions).*

- *PGI-Severity and PGI-Leakage are appropriate anchor scales for the concept of UUI episodes.*
- *PGI-Severity is an appropriate anchor scale for the concept of urgency.*

A summary of the anchor-based findings for Study 008 are as follows:

- For urinary frequency, a threshold for meaningful within-patient score change in average daily number of micturitions appears to fall somewhere in the range of -2.3 to -2.5 based on the eCDF curves (using PGI-Frequency anchor scale). Refer to Appendix H for eCDF curves.
- For UUI episodes, a threshold for meaningful within-patient percent change in average daily UUI episodes appears to be ~-90% based on the eCDF curves (using PGI-Leakage anchor scale). Refer to Appendix I for eCDF curves.
- For urgency episodes, a threshold for meaningful within-patient percent change in average daily urgency episodes appears to fall somewhere in the range of -65% to -70% based on the eCDF curves (using PGI-Frequency anchor scale). Refer to Appendix J for eCDF curves.

Interpretation of eCDF curves for Study 3003 were based on the 1 to 2 category improvement groups. The observed ranges were adjusted based on tolerable misclassification rates using no category and 1-category worsening curves. A summary of the anchor-based findings for Study 3003 are as follows:

- For urinary frequency, a meaningful within-patient score change in average daily number of micturitions appears to fall somewhere in the range of -3.0 to -3.5 (per misclassification rates of (a) ~ 20% of patients who experienced no change, and (b) ~ 14% of patients who experienced 1-category worsening) based on the eCDF curves (using Patient Global Impression (PGI)-Severity anchor scale; patients deemed a 1-category change on the PGI-Severity anchor scale as a meaningful improvement). Based on the PGI- Frequency anchor scale, a meaningful within-patient score change in average daily number of micturitions appears to fall somewhere in the range of -2.7 to -3.0 (per misclassification rates of (a) ~ 20% of patients who experienced no change, and (b) ~ 13% of patients who experienced 1-category worsening). Refer to Appendices K and L for eCDF curves.
- For UUI episodes, a meaningful within-patient percent change in average daily UUI episodes appears to be ~-90% (per misclassification rates of (a) ~ 20% of patients who experienced no change, and (b) ~ 15% of patients who experienced 1-category worsening) based on the eCDF curves (using PGI-Severity anchor scale). Based on the PGI- Leakage anchor scale, a meaningful within-patient percent change in average daily UUI episodes appears to be ~-89% (per misclassification rates of (a) ~ 15% of patients who experienced no change, and (b) ~ 15% of patients who experienced 1-category worsening). Refer to Appendices M and N for eCDF curves.
- For urgency episodes, a meaningful within-patient percent change in average daily urgency episodes appears to be ~-61% (per misclassification rates of (a) ~ 20% of patients who experienced no change, and (b) ~ 11% of patients who experienced 1-category worsening) based on the eCDF curves (using PGI-Severity anchor scale). Refer to Appendix O for eCDF curves.

Reviewer's comment(s):

- *Based on Study 3003 data, when you look at the aforementioned ranges, there is minimal separation between the treatment and the placebo arm (see Appendix R).*
- *Based on Study 3003 data, of the 382 patients treated with vibegron, 35.3% had ≥90% reduction in the average daily number of UUI episodes at 12 weeks compared to 23.7% of patients (n=371) receiving placebo. Based on the responder analysis in Study 3003, the applicant reports the following:*
    - *Of the 403 OAB Wet patients treated with GEMTESA 75 mg, 52% had ≥75% reduction in the average daily number of urge urinary incontinence episodes at 12 weeks compared to 37% of patients (n=405) receiving placebo.*
    - *Of the 403 OAB Wet patients treated with GEMTESA 75 mg, 29% had a 100% reduction in the average daily number of urge urinary incontinence episodes at 12 weeks compared to 23% of patients (n=405) receiving placebo.*
- *Based on Study 3003 data, of the 492 patients treated with vibegron, 33.7% had ≥60% reduction in the average daily number of urgency episodes at 12 weeks compared to 28.1% of patients (n=474) receiving placebo. Based on the responder analysis in Study 3003, the applicant reports the following:*
    - *Of the 526 patients treated with GEMTESA, 43% had ≥50% reduction in the average daily number of urgency episodes at 12 weeks compared to 38% of patients (n=520) receiving placebo.*
- *Note that different anchors were administered in Phase 2 trial versus Phase 3 trial, which may have contributed to the observed difference in clinically meaningful within-patient thresholds for endpoints on micturition, UUI episodes and urgency episodes between Phase 2 and Phase 3 Studies.*

The applicant also used qualitative methods to help inform the responder thresholds. Based on qualitative interviews conducted with 11 OAB patients in August 2017, a threshold of 50% reduction was found to be reasonable for urgency episodes, while a slightly higher threshold was needed for UUI episodes (e.g., >70% reduction). A 1-category improvement on the PGI-Severity anchor was deemed as a meaningful improvement by patients.

Reviewer's comment(s): *At the Type B meeting held January 18, 2018, the Agency agreed to a threshold of 75% for the endpoint definition of UUI and a threshold of 50% for urgency episodes.*

There were some concerns whether a one-category improvement would be considered a meaningful improvement on the PGI-Control and PGI-Frequency anchors as well. Specifically, there were concerns whether a subset of patients with severe symptoms (i.e., "no control" over OAB symptoms., "very often" accidental urine leakage) at baseline would consider moving one category change (i.e., "only a little control" and "often" respectively) as a clinically meaningful improvement.

At the Type B meeting, the Agency requested additional details on the sample size for patients in Study 008 who started out with "no control" at baseline and only had a 1-category improvement, and also requested the sample size for patients who started out with "very often" at baseline and had only a one category improvement. In the NDA submission, the applicant

provided data for each category change in the anchor scale. The majority of patients improved at least 2 or more categories (54%-69%) and most patients improved at least one category (81%-88%). However, the baseline severity (e.g., "no control," "very often") for the patients who experienced a 1-category improvement in each anchor scale of interest was not provided. Therefore, an IR was sent to the applicant on August 28, 2020 to provide the sample size of patients who started out at severe categories and had a one-category improvement.

Based on the applicant's response to the IR, the following conclusions can be made:

- *For patients starting with "very often" accidental urine leakage (n=260), approximately 26% of patients experienced a 1-category improvement, and 31% of patients experienced a 2-category improvement.*
- *For patients starting with "no control" over OAB symptoms (n=73), approximately 20% of patients experienced a 1-category improvement and 35% experienced a 2-category improvement.*

In general, there is overall improvement seen throughout the different change scores in the anchor scale (e.g., 1-category change, 2-category change, 3-category change). It is still unknown whether a 1-category change on the PGI-Control and PGI-Frequency anchor scales, as such this reviewer looked at each level of category change to derive a range of thresholds for each anchor scale. Refer to the summary of the results from the anchor-based analyses for Studies 008 and 3003.

OAB-q-LF-Coping domain

(b) (4)

Reviewer's comment(s): (b) (4)

(b) (4)

(b) (4)

Reviewer's comment(s): (b) (4)

(b) (4)

This reviewer does not agree with the proposed responder threshold (b) (4)

(b) (4)

(b) (4)

D. APPENDICES

Appendix A: Patient Voiding Diary (PVD)

Appendix B: Overactive Bladder Questionnaire (OAB-q) long form (LF) with One-Week Recall Period

Appendix C: Patient Global Impression of Severity (PGI-Severity)

Appendix D: Patient Global Impression of Change (PGI-Change)

Appendix E: Patient Global Impression of Control (PGI-Control)

Appendix F: Patient Global Impression of Symptom Frequency (PGI-Frequency)

Appendix G: Patient Global Impression of Urgency-Related Leakage (PGI-Leakage)

Appendix H: eCDF of Average Daily Micturition Change from Baseline to week 8 in study 008 (Phase 2) for All subjects by PGI-Frequency (Collapsed Categories)

Appendix I: eCDF of Average Number of UUI Episodes Percentage Change from Baseline to Week 8 in study 008 (Phase 2) for All Subjects by PGI-Leakage

Appendix J: eCDF of Average Number of Urgency Episodes Percentage Change from Baseline to Week 8 in study 008 (Phase 2) for All Subjects by PGI-Frequency

Appendix K: eCDF of Average Daily Micturition Change from Baseline to week 12 in Study 3003 (Phase 3) for All subjects by PGI-Severity (Collapsed Categories)

Appendix L: eCDF of Average Daily Micturition Change from Baseline to week 12 in Study 3003 (Phase 3) for All subjects by PGI-Frequency (Collapsed Categories)

Appendix M: eCDF of Average Number of UUI Episodes Percentage Change from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Severity

Appendix N: eCDF of Average Number of UUI Episodes Percentage Change from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Leakage

Appendix O: eCDF of Average Number of Urgency Episodes Percentage Change from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Severity

Appendix P: eCDF of OAB-q Coping Domain Transformed Change Score from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Severity (Collapsed Categories)

Appendix Q: eCDF of OAB-q Coping Domain Transformed Change Score from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Frequency (Collapsed Categories)

Appendix R: eCDF of Average Daily Micturitions Change from Baseline to Week 12 by Treatment in Study 3003 (Phase 3) by Treatment

Appendix S: eCDF of OAB-q Coping Domain Transformed Change Score from Baseline to Week 12 in Study 3003 (Phase 3) by Treatment

Appendix A: Patient Voiding Diary (PVD)

I started recording on this page when I got up for the day on:

Day of Week: ______________ Date: __ __ - __ __ - __ __ __ __ (D D - M M - Y Y Y Y)

What time did you get up for the day? __ __ : __ __ AM ☐ PM ☐

If you check ACCIDENTAL URINE LEAKAGE, remember to check ONE of three boxes for MAIN REASON FOR LEAKAGE

TIME (Please write in the time and check a.m or p.m.)	NEED TO URINATE IMMEDIATELY (Check if you felt a need to urinate immediately.)	URINATED IN TOILET	ACCIDENTAL URINE LEAKAGE (Check if you had leakage of any amount.)	MAIN REASON FOR LEAKAGE (If you had any leakage, check the main reason.)
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
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__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other

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If you check ACCIDENTAL URINE LEAKAGE, remember to check ONE of three boxes for MAIN REASON FOR LEAKAGE

TIME (Please write in the time and check a.m or p.m.)	NEED TO URINATE IMMEDIATELY (Check if you felt a need to urinate immediately.)	URINATED IN TOILET	ACCIDENTAL URINE LEAKAGE (Check if you had leakage of any amount.)	MAIN REASON FOR LEAKAGE (If you had any leakage, check the main reason.)
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other
__ __ : __ __ AM☐ PM☐	☐	☐	☐ →	☐ Urge ☐ Stress ☐ Other

Continue recording on this page even if you wake up during the night or early morning. Start a new page tomorrow when you get up for the day.

What time did you go to bed for the night? __ __ : __ __ AM☐ PM☐

Did you record each time you urinated or leaked during this Diary Day? Yes ☐ No ☐

I confirm that the information on this form is accurate.	Patient's Initials:	Date:
STUDY COORDINATOR USE ONLY	***I have reviewed this information.*** Staff's initials:	Date:

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Appendix B: Overactive Bladder Questionnaire (OAB-q) long form (LF) with One-Week

(b) (4)

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Appendix C: Patient Global Impression of Severity (PGI-Severity)

Patient Global Impression of Severity (PGI-Severity)

1. Over the past week, how would you rate your overactive bladder symptoms?

☐ None

☐ Mild

☐ Moderate

☐ Severe

Appendix D: Patient Global Impression of Change (PGI-Change)

5. Overall, compared to the start of the study, how would you rate your overactive bladder symptoms over the past week?

☐ Much better

☐ Moderately better

☐ A little better

☐ No change

☐ A little worse

☐ Moderately worse

☐ Much worse

Appendix E: Patient Global Impression of Control (PGI-Control)

Patient Global Impression of Control (PGI-Control)

2. Over the past week, how much control did you have over your overactive bladder symptoms?

☐ Complete control

☐ A lot of control

☐ Some control

☐ Only a little control

☐ No control

Appendix F: Patient Global Impression of Symptom Frequency (PGI-Frequency)

3. Over the past week, how often did you have overactive bladder symptoms?

☐ Never

☐ Rarely

☐ Sometimes

☐ Often

☐ Very often

Appendix G: Patient Global Impression of Urgency-Related Leakage (PGI-Leakage)

4. Over the past week, how often did you have accidental urine leakage?

☐ Never

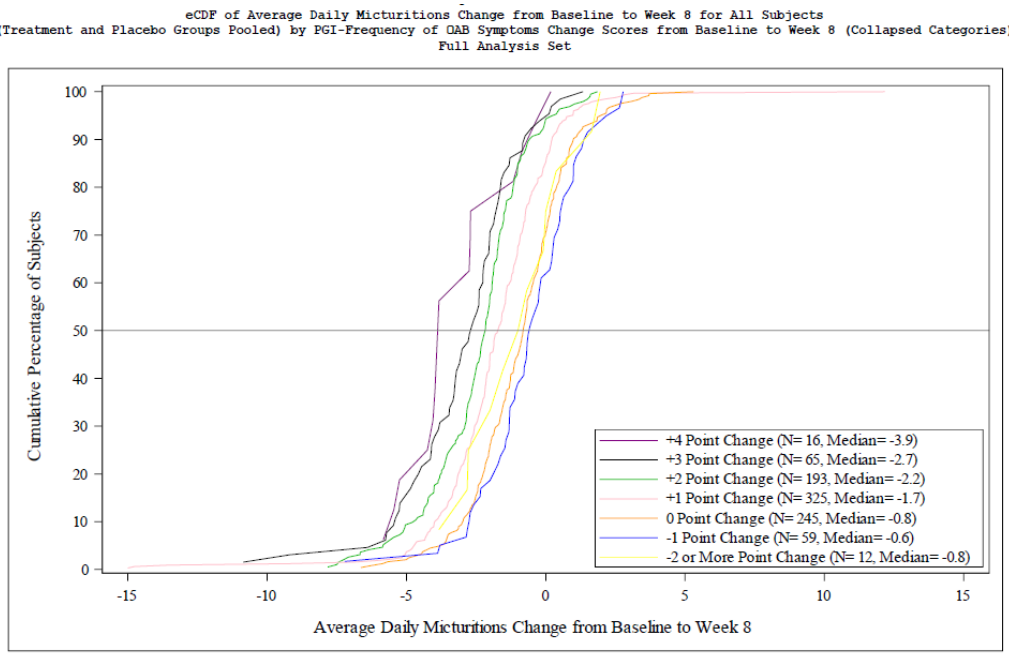
☐ Rarely

☐ Sometimes

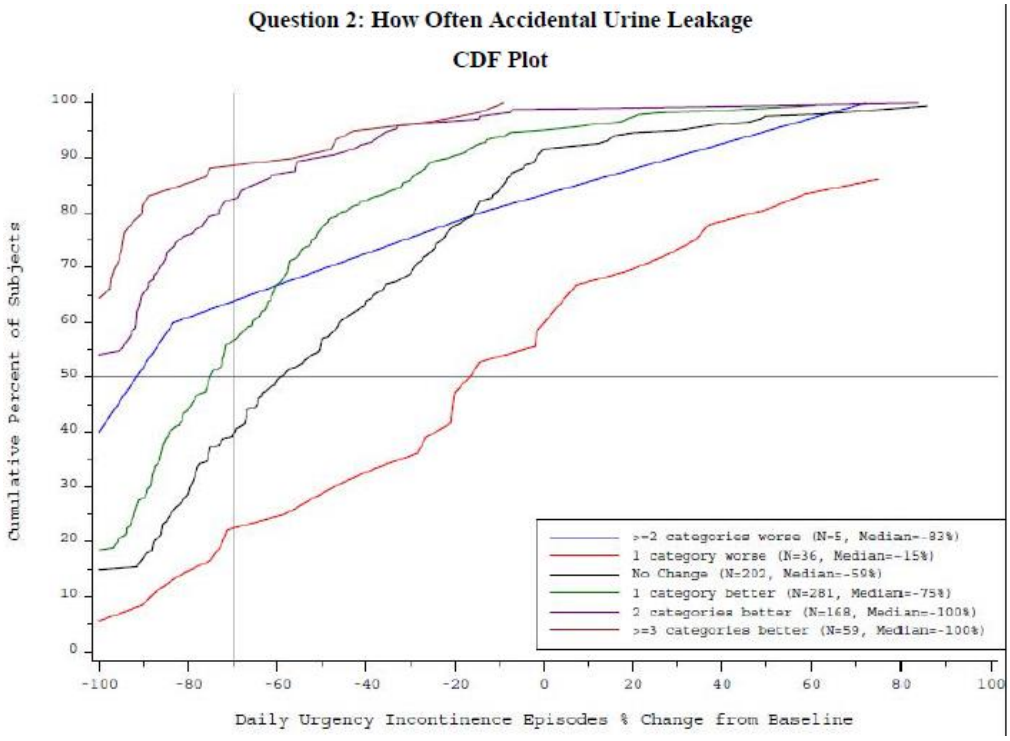
☐ Often

☐ Very often

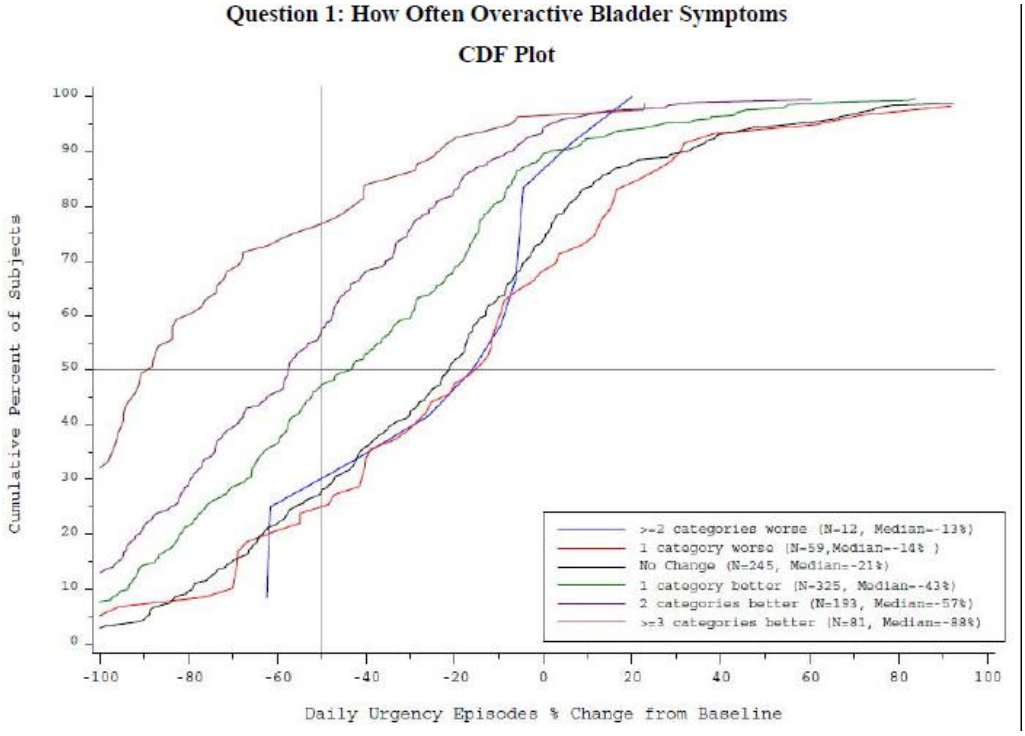
Appendix H: eCDF curves of Average Daily Micturition Change from Baseline to week 8 in study 008 (Phase 2) for All subjects by PGI-Frequency (Collapsed Categories)



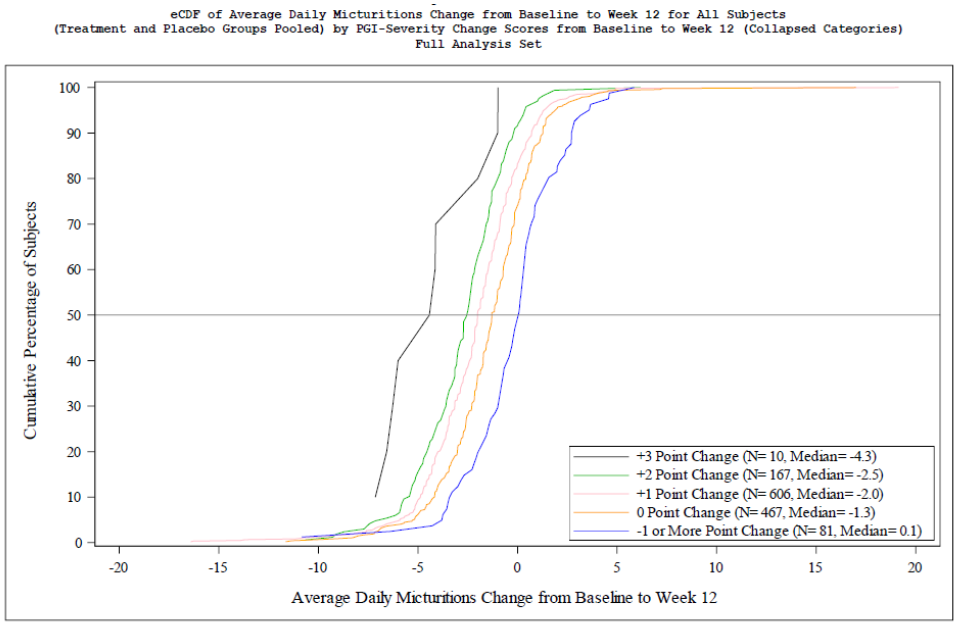
Appendix I: eCDF Curve of Average Number of UUI episodes Percentage Change from Baseline to Week 8 in study 008 (Phase 2) for All Subjects by PGI-Leakage



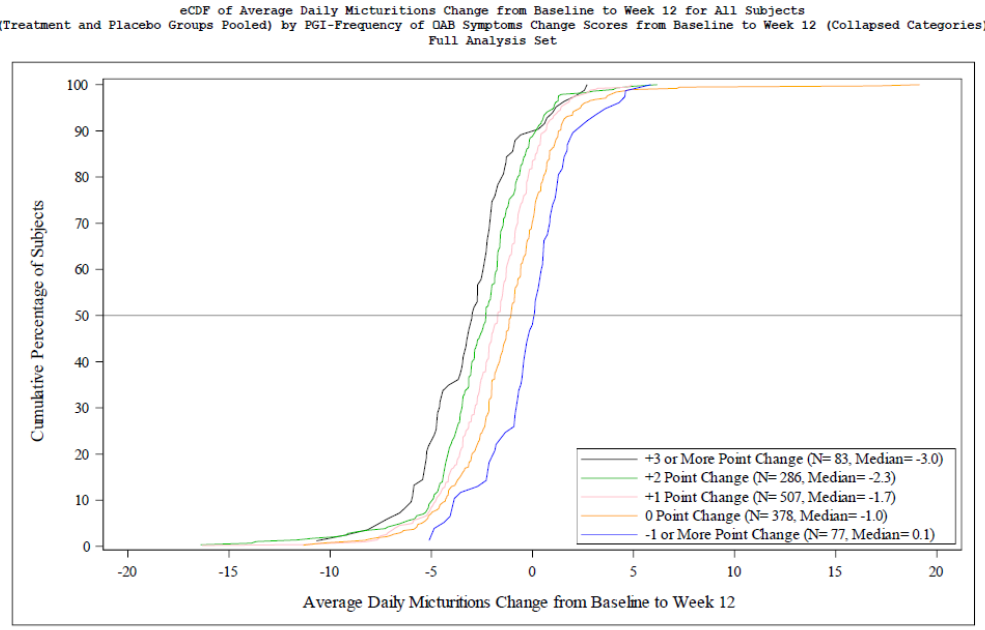
Appendix J: eCDF Curves of Average Number of Urgency Episodes Percentage Change from Baseline to Week 8 in study 008 (Phase 2) for All Subjects by PGI-Frequency



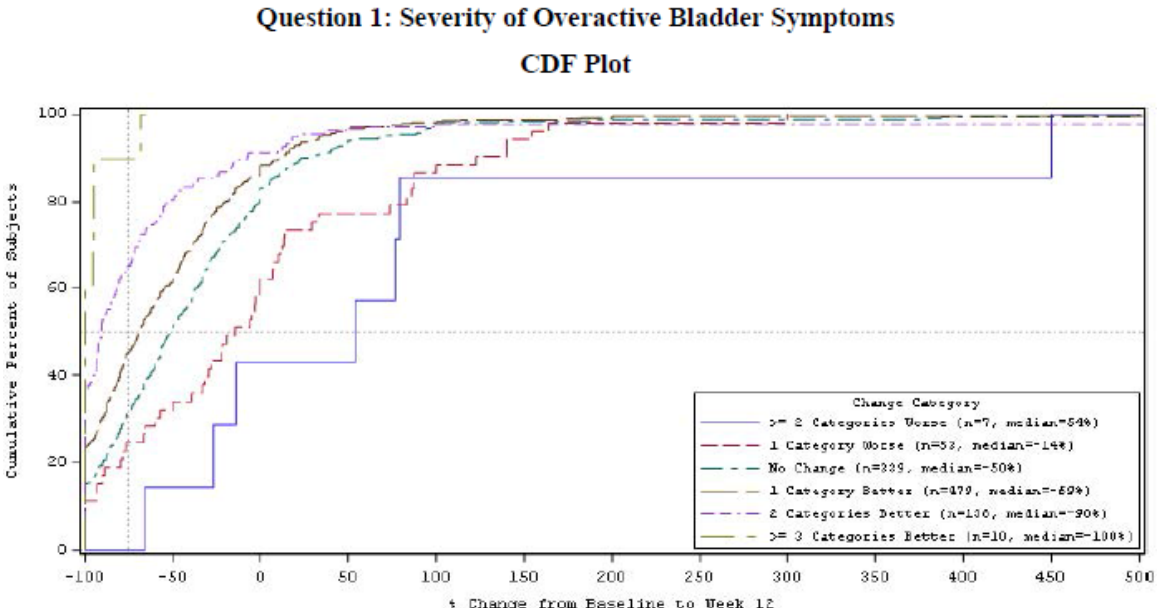
Appendix K: eCDF curves for Average Daily Micturition Change from Baseline to week 12 in Study 3003 (Phase 3) for All subjects by PGI-Severity (Collapsed Categories)



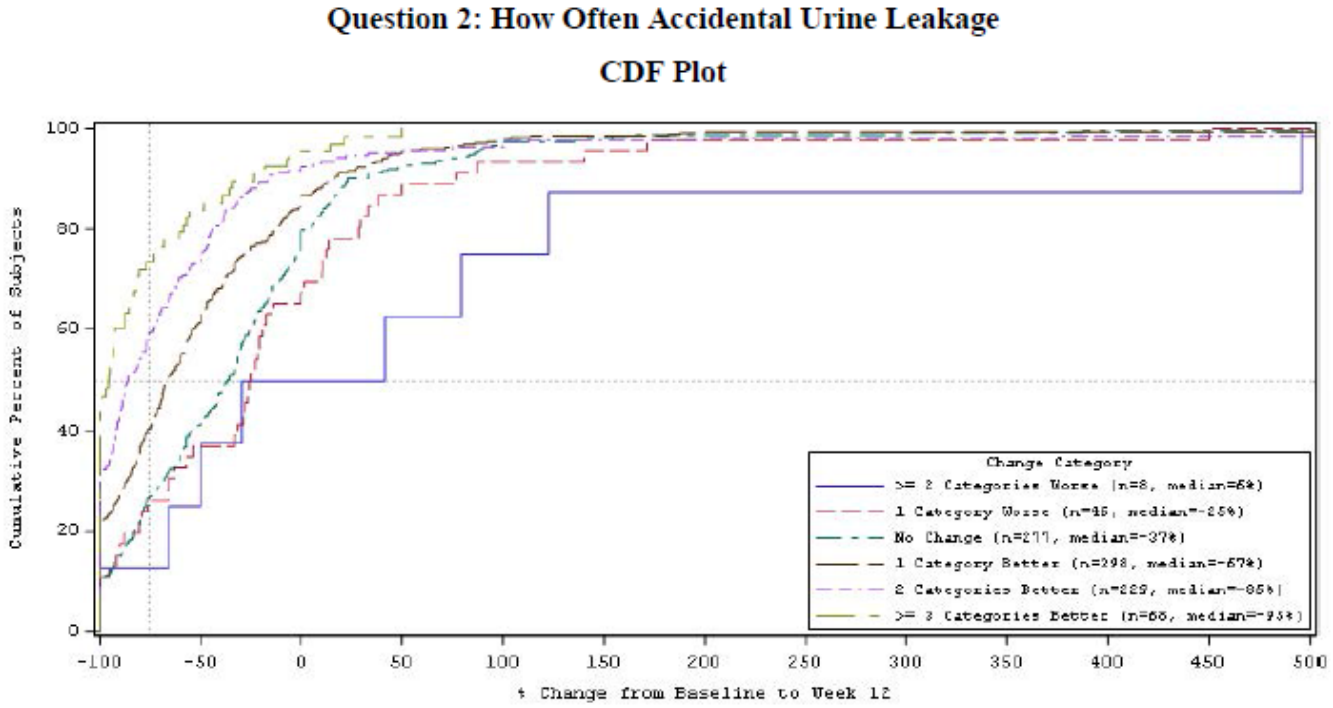
Appendix L: eCDF curves for Average Daily Micturition Change from Baseline to week 12 in Study 3003 (Phase 3) for All subjects by PGI-Frequency (Collapsed Categories)



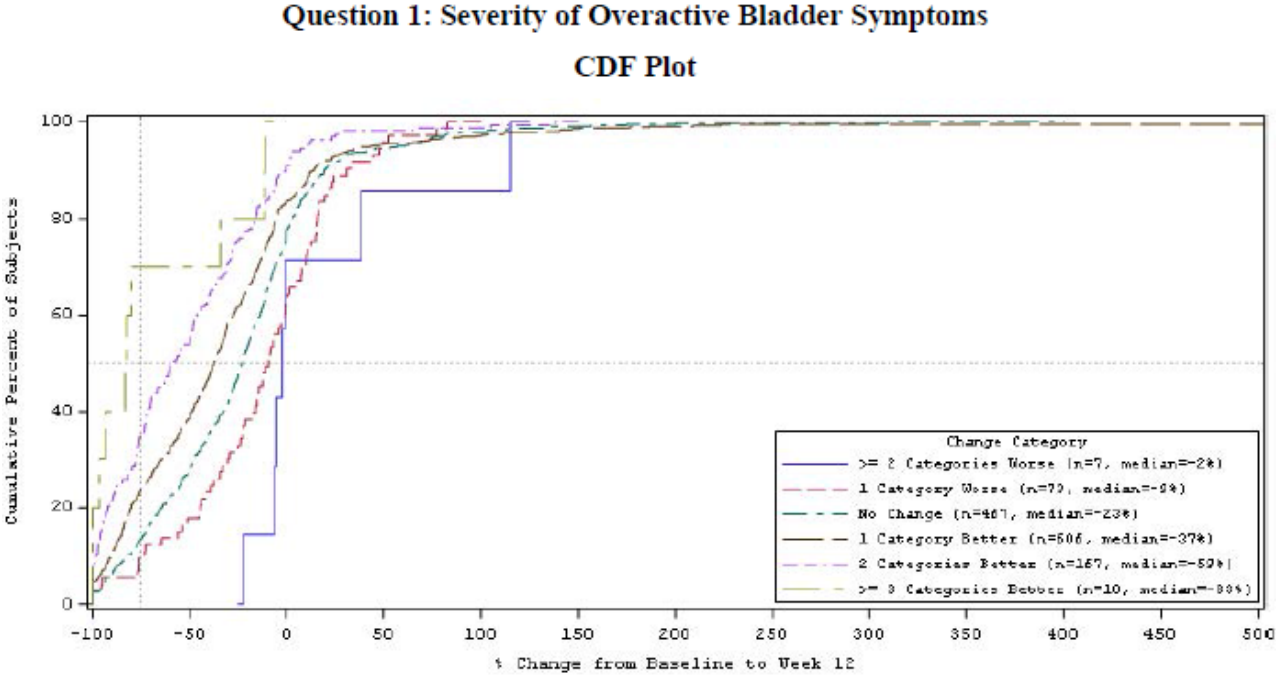
Appendix M: eCDF curves of Average Number of UUI Episodes Change from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Severity



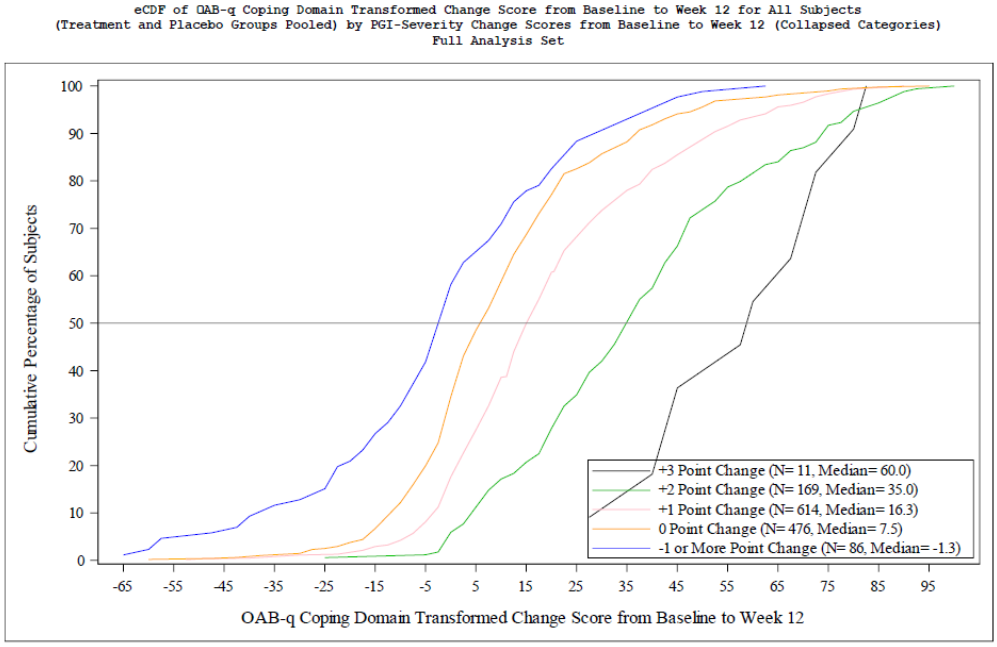
Appendix N: eCDF Curves of Average Number of UUI Episodes Percentage Change from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Leakage



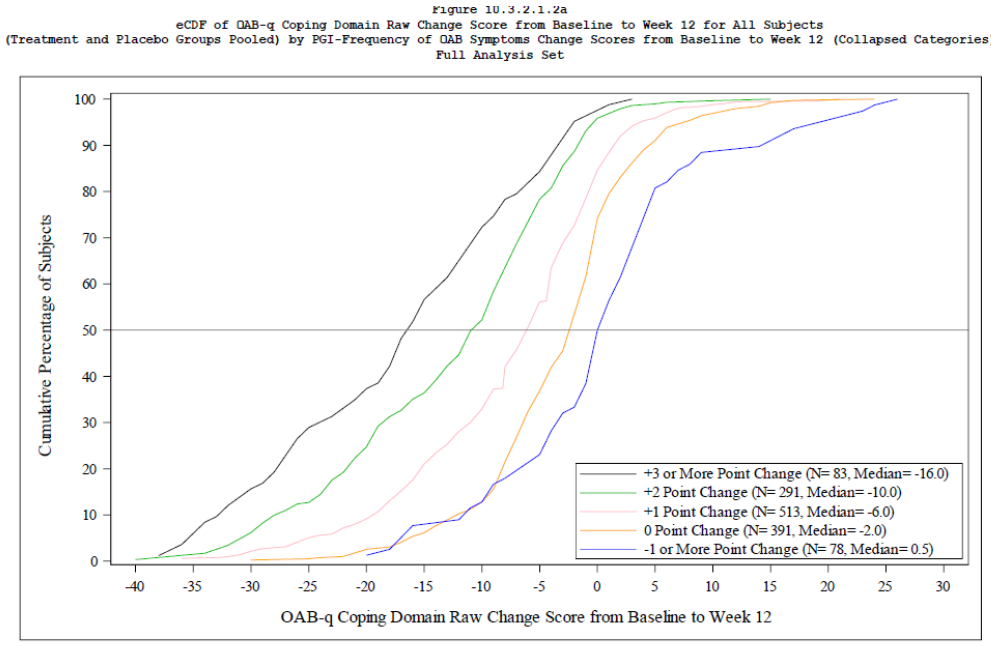
Appendix O: eCDF curves of Average Number of Urgency Episodes Percentage Change from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Severity



Appendix P: eCDF of OAB-q Coping Domain Transformed Change Score from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Severity (Collapsed Categories)



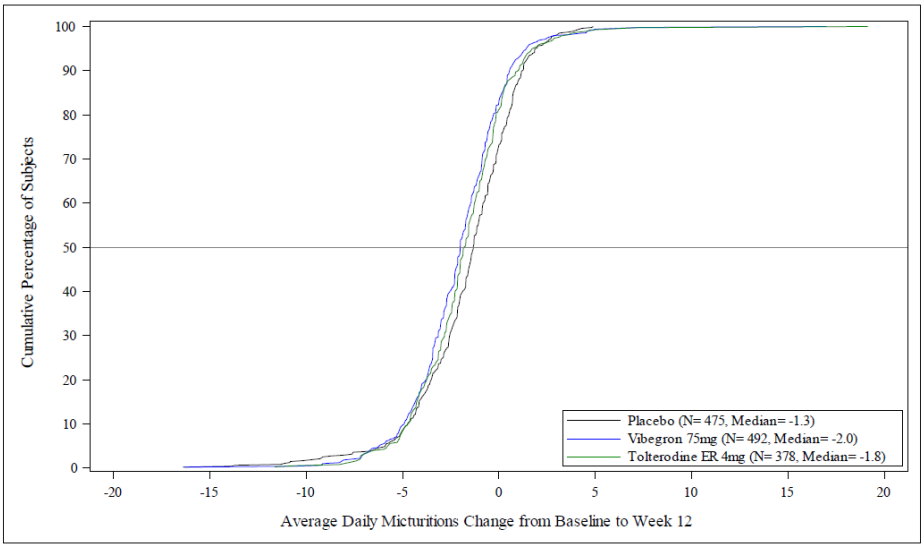
Appendix Q: eCDF of OAB-q Coping Domain Transformed Change Score from Baseline to Week 12 in Study 3003 (Phase 3) for All Subjects by PGI-Frequency (Collapsed Categories)



Appendix R: eCDF of Average Daily Micturitions Change from Baseline to Week 12 by Treatment in Study 3003 (Phase 3) by Treatment

FDA Request #10

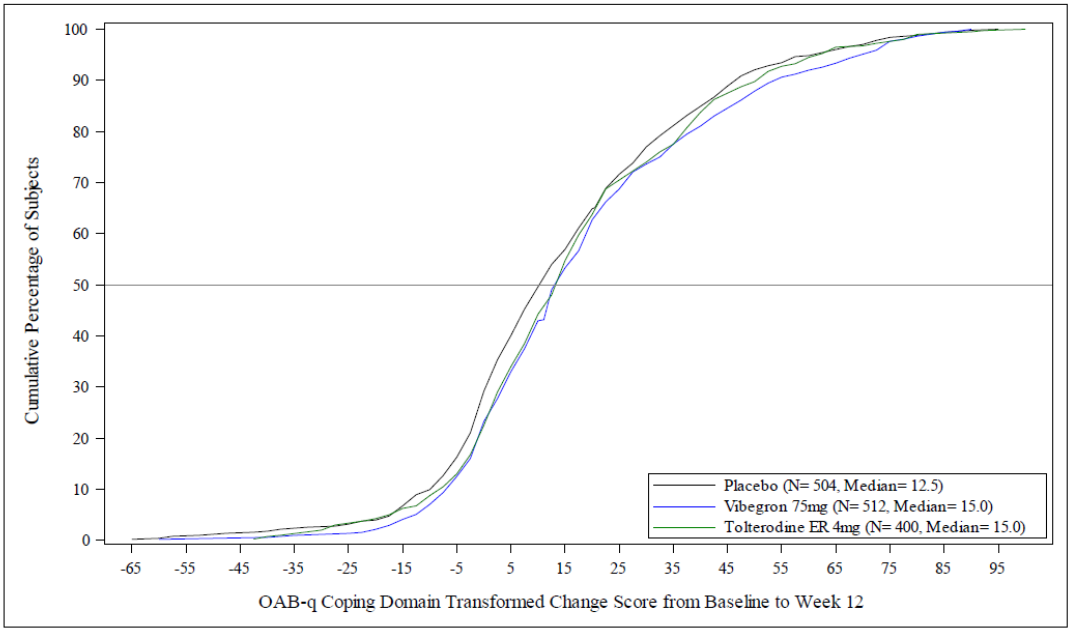
Figure 10.9.2.1
eCDF of Average Daily Micturitions Change from Baseline to Week 12 by Treatment
Full Analysis Set



Appendix S: eCDF of OAB-q Coping Domain Transformed Change Score from Baseline to Week 12 in Study 3003 (Phase 3) by Treatment

FDA Request #10

Figure 10.8.2.1
eCDF of OAB-q Coping Domain Change from Baseline to Week 12 by Treatment
Full Analysis Set



Note: If < 50% of items are available, the subscore is regarded as missing; however if >= 50% of items are available, the subscore includes missing items imputed as the average of the remaining non-missing items for the subscore.
SAS Program: F_10_8_2_X.sas, Generated: 09SEP2020T15:02

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/

PARIMA S GHAFOORI
10/14/2020 12:22:05 PM

SELENA R DANIELS
10/14/2020 01:04:48 PM

ELEKTRA J PAPADOPOULOS
10/14/2020 09:42:01 PM
Agree with the content of this review. However, I would like to clarify that the content of the OAB-q LF Coping domain is not specific to OAB-Dry patients (see page 4). However, it may not have complete concept coverage in patients with OAB.