Clinical trial results:
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

Summary

EudraCT number	2017-003293-14
Trial protocol	LV HU EE BG LT
Global end of trial date	04 February 2019

Results information

Result version number	v2 (current)
This version publication date	19 March 2021
First version publication date	27 January 2021
Version creation reason	• Correction of full data set Alignment with ClinicalTrials.gov summary.

Trial information

Trial identification

Sponsor protocol code	RVT-901-3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03492281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Urovant Sciences GmbH
Sponsor organisation address	Viaduktstrasse 8 4051, Basel, Switzerland,
Public contact	Clinical Trial Information Contact, Urovant Sciences GmbH, 41 (42) 2155999, info@urovant.com
Scientific contact	Clinical Trial Information Contact, Urovant Sciences GmbH, 41 (42) 2155999, info@urovant.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2019
Global end of trial reached?	Yes
Global end of trial date	04 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to evaluate the efficacy of vibegron compared to placebo in subjects with symptoms of overactive bladder (OAB), specifically the frequency of micturitions and frequency of urge urinary incontinence episodes, and to evaluate the safety and tolerability of treatment with vibegron.

Protection of trial subjects:

Each investigator obtained approval of the study from a properly constituted Institutional Review Board (IRB), Research Ethics Board (REB), or Independent Ethics Committee (IEC) prior to study initiation. This study was conducted in compliance with Good Clinical Practice (GCP). Prior to participating in any study procedures, the study was discussed with each subject and/or with the subject's legally authorized representative, and written informed consent was obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Lithuania: 3
Country: Number of subjects enrolled	Poland: 82
Country: Number of subjects enrolled	United States: 1363
Worldwide total number of subjects	1518
EEA total number of subjects	129

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	871
From 65 to 84 years	632
85 years and over	15

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 3149 subjects screened for this study, 1518 were randomized (after a 2-week, single-blind placebo Run-in Period), and 1515 received 1 dose of double-blind study drug in the Treatment Period (Safety Set: placebo, N = 540; vibegron, N = 545; tolterodine, N = 430).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received matching placebo, orally, once daily for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match vibegron 75-mg tablet, administered as a single tablet, orally, once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match tolterodine extended release (ER) 4-mg capsule, administered as a single capsule, orally, once daily

Arm title	Vibegron 75 mg

Arm description:

Subjects received vibegron 75 milligrams (mg), orally, once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Vibegron
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vibegron 75-mg tablet, administered as a single tablet, orally, once daily

Arm title	Tolterodine ER 4 mg

Arm description:

Subjects received tolterodine ER 4 mg, orally, once daily for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Tolterodine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tolterodine ER 4-mg capsule, administered as a single capsule, orally, once daily

Number of subjects in period 1[1]	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Started	540	545	430
Completed	486	502	385
Not completed	54	43	45
Withdrawn Due To Sponsor	1	-	1
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	21	14	13
Physician decision	1	-	3
Adverse event, non-fatal	6	8	13
Lost to follow-up	14	15	10
Captured As Other In Database	8	6	3
Lack of efficacy	3	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of 3149 subjects screened for this study, 1518 were randomized, and 1515 received 1 dose of double-blind study drug in the Treatment Period (Safety Set). Baseline data are reported for members of the Safety Set.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo, orally, once daily for 12 weeks.	
Reporting group title	Vibegron 75 mg
Reporting group description:	
Subjects received vibegron 75 milligrams (mg), orally, once daily for 12 weeks.	
Reporting group title	Tolterodine ER 4 mg
Reporting group description:	
Subjects received tolterodine ER 4 mg, orally, once daily for 12 weeks.	

Reporting group values	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Number of subjects	540	545	430
Age categorical Units:			
Age continuous Units: years			
arithmetic mean	59.9	60.4	59.8
standard deviation	± 13.35	± 13.49	± 13.27
Gender categorical Units: Subjects			
Female	459	463	364
Male	81	82	66
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska	3	2	0
Asian	30	28	27
Black or African American	85	78	72
White	418	435	326
Puerto Rican	1	1	1
White and Black or African American	1	0	0
Hispanic	2	1	0
Filipino	0	0	1
Morrocan	0	0	1
Multiracial	0	0	1
White, Black or African American	0	0	1
Average number of micturitions per 24 hours in all overactive bladder (OAB) subjects			
A micturition/void was defined as "Urinated in Toilet" as indicated on the Patient Voiding Diary (PVD). The number of micturitions was defined as the number of times a subject voided in the toilet as indicated on the PVD. The average daily number of micturitions was calculated using the daily entries in the PVD (which was to be completed prior to each study visit) as the total number of micturitions that occurred on a Complete Diary Day (CDD) divided by the number of CDDs in the PVD. n=537, 544, and 430 for Placebo, Vibegron 75 mg, and Tolterodine ER 4 mg, respectively.			
Units: micturitions per 24 hours			
arithmetic mean	11.72	11.38	11.53

standard deviation	± 3.971	± 3.508	± 3.184
Average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet subjects			
The number of UUI episodes was defined as the number of times a subject had checked "urge" as the main reason for the leakage in the PVD, regardless of whether more than one reason for leakage in addition to "urge" was checked. OAB Wet subjects were those subjects with an average of ≥8.0 micturitions per Diary Day (DD); with an average of ≥1.0 UUI episodes per DD; and, if stress urinary incontinence was present, with a total number of UUI episodes greater than the total number of stress urinary incontinence episodes from the previous visit diary. n=537, 544, and 430.			
Units: UUI episodes per 24 hours			
arithmetic mean	2.80	2.78	2.72
standard deviation	± 2.978	± 3.10	± 2.616

Reporting group values	Total		
Number of subjects	1515		
Age categorical			
Units:			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	1286		
Male	229		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska	5		
Asian	85		
Black or African American	235		
White	1179		
Puerto Rican	3		
White and Black or African American	1		
Hispanic	3		
Filipino	1		
Morrocan	1		
Multiracial	1		
White, Black or African American	1		
Average number of micturitions per 24 hours in all overactive bladder (OAB) subjects			
A micturition/void was defined as "Urinated in Toilet" as indicated on the Patient Voiding Diary (PVD). The number of micturitions was defined as the number of times a subject voided in the toilet as indicated on the PVD. The average daily number of micturitions was calculated using the daily entries in the PVD (which was to be completed prior to each study visit) as the total number of micturitions that occurred on a Complete Diary Day (CDD) divided by the number of CDDs in the PVD. n=537, 544, and 430 for Placebo, Vibegron 75 mg, and Tolterodine ER 4 mg, respectively.			
Units: micturitions per 24 hours			
arithmetic mean			
standard deviation	-		
Average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet subjects			

The number of UUI episodes was defined as the number of times a subject had checked "urge" as the main reason for the leakage in the PVD, regardless of whether more than one reason for leakage in addition to "urge" was checked. OAB Wet subjects were those subjects with an average of ≥8.0 micturitions per Diary Day (DD); with an average of ≥1.0 UUI episodes per DD; and, if stress urinary incontinence was present, with a total number of UUI episodes greater than the total number of stress urinary incontinence episodes from the previous visit diary. n=537, 544, and 430.			
Units: UUI episodes per 24 hours arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo, orally, once daily for 12 weeks.	
Reporting group title	Vibegron 75 mg
Reporting group description:	
Subjects received vibegron 75 milligrams (mg), orally, once daily for 12 weeks.	
Reporting group title	Tolterodine ER 4 mg
Reporting group description:	
Subjects received tolterodine ER 4 mg, orally, once daily for 12 weeks.	
Subject analysis set title	Placebo: Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received matching placebo, orally, once daily for 12 weeks. The Full Analysis Set is defined as all randomized OAB subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from baseline micturition measurement.	
Subject analysis set title	Vibegron 75 mg: Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received vibegron 75 milligrams (mg), orally, once daily for 12 weeks. The Full Analysis Set is defined as all randomized OAB Subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from baseline micturition measurement.	
Subject analysis set title	Tolterodine ER 4 mg: Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received tolterodine extended release (ER) 4 mg, orally, once daily for 12 weeks. The Full Analysis Set is defined as all randomized OAB subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from baseline micturition measurement.	
Subject analysis set title	Placebo: OAB Wet
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who met the definition of OAB Wet at study entry (based on the PVD) received matching placebo, orally, once daily for 12 weeks. OAB Wet subjects were defined as those with an average of ≥8.0 micturitions per Diary Day; with an average of ≥1.0 UUI episodes per Diary Day; and, if stress urinary incontinence was present, with a total number of UUI episodes greater than the total number of stress urinary incontinence episodes from the previous visit diary. Analysis was conducted in members of the Full Analysis Set for Incontinence (FAS-I) Population, comprised of all randomized OAB Wet subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from the Baseline UUI measurement.	
Subject analysis set title	Vibegron 75 mg: OAB Wet
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who met the definition of OAB Wet at study entry (based on the PVD) received vibegron 75 milligrams (mg), orally, once daily for 12 weeks. OAB Wet subjects were defined as those with an average of ≥8.0 micturitions per Diary Day; with an average of ≥1.0 UUI episodes per Diary Day; and, if stress urinary incontinence was present, with a total number of UUI episodes greater than the total number of stress urinary incontinence episodes from the previous visit diary. Analysis was conducted in members of the FAS-I Population, comprised of all randomized OAB Wet subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from the Baseline UUI measurement.	
Subject analysis set title	Tolterodine ER 4 mg: OAB Wet
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who met the definition of OAB Wet at study entry (based on the PVD) received tolterodine	

extended release (ER) 4 mg, orally, once daily for 12 weeks. OAB Wet subjects were defined as those with an average of ≥8.0 micturitions per Diary Day; with an average of ≥1.0 UUI episodes per Diary Day; and, if stress urinary incontinence was present, with a total number of UUI episodes greater than the total number of stress urinary incontinence episodes from the previous visit diary. Analysis was conducted in members of the FAS-I Population, comprised of all randomized OAB Wet subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from the Baseline UUI measurement.

Primary: Change from Baseline (CFB) at Week 12 in the average number of micturitions per 24 hours in all overactive bladder (OAB) subjects

End point title	Change from Baseline (CFB) at Week 12 in the average number of micturitions per 24 hours in all overactive bladder (OAB) subjects

End point description:

A micturition/void is defined as "Urinated in Toilet" as indicated on the PVD. The number of micturitions is defined as the number of times a subject voided in the toilet as indicated on the PVD. The average daily number of micturitions was calculated using the daily entries in the PVD (which was to be completed prior to each study visit) as the total number of micturitions that occurred on a Complete Diary Day (CDD) divided by the number of CDDs in the PVD. CFB was calculated as the post-BL value minus the BL value. "Per 24 hours" corresponds to one Diary Day (i.e., time between when the subject got up for the day each morning and time the sujbject got up for the day the next morning as recorded in the PVD). Covariates included in the mixed model for repeated measures are study visit (Weeks 2, 4, 8, and 12), OAB type (wet/dry), sex, region (U.S./non-U.S.), BL number of micturitions, and treatment by study visit interaction. FAS=Full Analysis Set.

End point type	Primary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	475[1]	492[2]	378[3]	
Units: micturitions per 24 hours				
least squares mean (standard error)	-1.3 (± 0.14)	-1.8 (± 0.14)	-1.6 (± 0.15)	

Notes:

[1] - FAS. Only subjects with evaluable data were analyzed.

[2] - FAS. Only subjects with evaluable data were analyzed.

[3] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo

Statistical analysis description:

LS=least squares

Comparison groups	Placebo: Full Analysis Set v Vibegron 75 mg: Full Analysis Set
Number of subjects included in analysis	967
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[4] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0988 [5]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[5] - Comparisons between tolterodine ER and placebo are considered descriptive.

Primary: CFB at Week 12 in the average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet subjects

End point title	CFB at Week 12 in the average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet subjects

End point description:

The number of UUI episodes is defined as the number of times a subject had checked "urge" as the main reason for the leakage in the PVD, regardless of whether more than one reason for leakage in addition to "urge" was checked. The average daily number of UUI episodes was calculated using the daily entries in the PVD (which was to be completed prior to each study visit) as the total number of UUI episodes that occurred on a CDD divided by the number of CCDs in the PVD. CFB was calculated as the post-BL value minus the BL value. "Per 24 hours" corresponds to one Diary Day (i.e., time between when subject got up for the day each morning and time subject got up for the day the next morning as recorded in the PVD). Covariates included in the mixed model for repeated measures were study visit (Weeks 2, 4, 8, and 12), sex, region (U.S./non-U.S.), BL number of UUI episodes and treatment by study visit interaction. FAS-I=Full Analysis Set for Incontinence.

End point type	Primary

End point timeframe:

Baseline; Week 12

End point values	Placebo: OAB Wet	Vibegron 75 mg: OAB Wet	Tolterodine ER 4 mg: OAB Wet	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	372[6]	383[7]	286[8]	
Units: UUI episodes per 24 hours				
least squares mean (standard error)	-1.4 (± 0.13)	-2.0 (± 0.13)	-1.8 (± 0.14)	

Notes:

[6] - FAS-I. Only those subjects with evaluable data were analyzed.

[7] - FAS-I. Only those subjects with evaluable data were analyzed.

[8] - FAS-I. Only those subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: OAB Wet v Placebo: OAB Wet
Number of subjects included in analysis	755
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[9] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: OAB Wet v Placebo: OAB Wet
Number of subjects included in analysis	658
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123 [10]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[10] - Comparisons between tolterodine ER and placebo are considered descriptive.

Secondary: CFB at Week 12 in the average number of urgency episodes over 24 hours in all OAB subjects

End point title	CFB at Week 12 in the average number of urgency episodes over 24 hours in all OAB subjects

End point description:

An urgency episode is defined as the "Need to Urinate Immediately" as indicated on the PVD. CFB is calculated as the post-BL value minus the BL value. "Over 24 hours" corresponds to one Diary Day (i.e., time between when the subject got up for the day each morning and time the subject got up for the day the next morning as recorded in the PVD). Covariates included in the mixed model for repeated measures were study visit (Weeks 2, 4, 8, and 12), OAB type (wet/dry), sex, region (U.S./non-U.S.), BL number of urgency episodes, and treatment by study visit interaction.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	475[11]	492[12]	378[13]	
Units: urgency episodes over 24 hours				
least squares mean (standard error)	-2.0 (± 0.19)	-2.7 (± 0.19)	-2.5 (± 0.21)	

Notes:

[11] - FAS. Only subjects with evaluable data were analyzed.

[12] - FAS. Only subjects with evaluable data were analyzed.

[13] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	967
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [14]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[14] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set

Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0648 [15]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[15] - Comparisons between tolterodine ER and placebo are considered descriptive.

Secondary: Percentage of OAB Wet subjects with at least a 75% reduction from Baseline in UUI episodes per 24 hours at Week 12

End point title	Percentage of OAB Wet subjects with at least a 75% reduction from Baseline in UUI episodes per 24 hours at Week 12

End point description:

The number of UUI episodes is defined as the number of times a subject had checked "urge" as the main reason for the leakage in the PVD, regardless of whether more than one reason for leakage in addition to "urge" was checked. The average daily number of UUI episodes was calculated using the daily entries in the PVD (which was to be completed prior to each study visit) as the total number of UUI episodes that occurred on a CDD divided by the number of CCDs in the PVD. CFB was calculated as the post-BL value minus the BL value. "Per 24 hours" corresponds to one Diary Day (i.e., time between when subject got up for the day each morning and time subject got up for the day the next morning as recorded in the PVD).

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: OAB Wet	Vibegron 75 mg: OAB Wet	Tolterodine ER 4 mg: OAB Wet	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	405[16]	403[17]	319[18]	
Units: percentage of subjects				
number (not applicable)				
Unadjusted	36.8	52.4	47.6	
Adjusted for sex	32.8	49.3	42.2	

Notes:

[16] - FAS-I. The multiple imputation method was used for missing values.

[17] - FAS-I. The multiple imputation method was used for missing values.

[18] - FAS-I. The multiple imputation method was used for missing values.

Statistical analyses

Statistical analysis title	Difference in Percentage: Vibegron 75 mg:Placebo
Comparison groups	Vibegron 75 mg: OAB Wet v Placebo: OAB Wet

Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.7
upper limit	23.4

Notes:

[19] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex (female/male), with weights proposed by Greenland and Robins.

Statistical analysis title	Difference in Percentage: Tolterodine ER:Placebo
Comparison groups	Tolterodine ER 4 mg: OAB Wet v Placebo: OAB Wet
Number of subjects included in analysis	724
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	16.7

Notes:

[20] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex (female/male), with weights proposed by Greenland and Robins.

Secondary: Percentage of OAB Wet subjects with a 100% reduction from Baseline in UUI episodes per 24 hours at Week 12

End point title	Percentage of OAB Wet subjects with a 100% reduction from Baseline in UUI episodes per 24 hours at Week 12

End point description:

The number of UUI episodes is defined as the number of times a subject had checked "urge" as the main reason for the leakage in the PVD, regardless of whether more than one reason for leakage in addition to "urge" was checked. The average daily number of UUI episodes was calculated using the daily entries in the PVD (which was to be completed prior to each study visit) as the total number of UUI episodes that occurred on a CDD divided by the number of CCDs in the PVD. CFB was calculated as the post-BL value minus the BL value. "Per 24 hours" corresponds to one Diary Day (i.e., time between when subject got up for the day each morning and time subject got up for the day the next morning as recorded in the PVD).

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: OAB Wet	Vibegron 75 mg: OAB Wet	Tolterodine ER 4 mg: OAB Wet	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	405[21]	403[22]	319[23]	
Units: percentage of subjects				
number (not applicable)				
Unadjusted	22.5	28.8	26.6	
Adjusted for sex	19.0	25.3	20.9	

Notes:

[21] - FAS-I. The multiple imputation method was used for missing values.

[22] - FAS-I. The multiple imputation method was used for missing values.

[23] - FAS-I. The multiple imputation method was used for missing values.

Statistical analyses

Statistical analysis title	Difference in Percentage: Vibegron 75 mg:Placebo
Comparison groups	Vibegron 75 mg: OAB Wet v Placebo: OAB Wet
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	12.1

Notes:

[24] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex (female/male), with weights proposed by Greenland and Robins.

Statistical analysis title	Difference in Percentage: Tolterodine ER:Placebo
Comparison groups	Tolterodine ER 4 mg: OAB Wet v Placebo: OAB Wet
Number of subjects included in analysis	724
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5447 [25]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	7.8

Notes:

[25] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex (female/male), with weights proposed by Greenland and Robins.

Secondary: Percentage of all OAB subjects with at least a 50% reduction from Baseline in urgency episodes per 24 hours at Week 12

End point title	Percentage of all OAB subjects with at least a 50% reduction from Baseline in urgency episodes per 24 hours at Week 12

End point description:

An urgency episode is defined as the "Need to Urinate Immediately" as indicated on the PVD. CFB is calculated as the post-BL value minus the BL value. "Per 24 hours" corresponds to one Diary Day (i.e., time between when the subject got up for the day each morning and time the subject got up for the day the next morning as recorded in the PVD).

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	520[26]	526[27]	417[28]	
Units: percentage of subjects				
number (not applicable)				
Unadjusted	38.3	43.2	41.2	
Adjusted for sex	32.8	39.5	36.4	

Notes:

[26] - FAS. The multiple imputation method was used for missing values.

[27] - FAS. The multiple imputation method was used for missing values.

[28] - FAS. The multiple imputation method was used for missing values.

Statistical analyses

Statistical analysis title	Difference in Percentage: Vibegron 75 mg:Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0235 [29]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	12.7

Notes:

[29] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex and OAB type (wet/dry), with weights proposed by Greenland and Robins.

Statistical analysis title	Difference in Percentage: Tolterodine ER:Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set

Number of subjects included in analysis	937
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [30]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	10

Notes:

[30] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex and OAB type (wet/dry), with weights proposed by Greenland and Robins.

Secondary: CFB at Week 12 in the average number of total incontinence episodes over 24 hours in OAB Wet subjects

End point title	CFB at Week 12 in the average number of total incontinence episodes over 24 hours in OAB Wet subjects

End point description:

Total incontinence is defined as having any reason for "Accidental Urine Leakage" and/or "Accidental Urine Leakage" checked, as indicated on the PVD. It is assumed that if the subject recorded a reason for leakage then the accidental urine leakage occurred. CFB is calculated as the post-BL value minus the BL value. "Over 24 hours" corresponds to one Diary Day (i.e., time between when the subject got up for the day each morning and time the subject got up for the day the next morning as recorded in the PVD). Covariates included in the mixed model for repeated measures were study visit (Weeks 2, 4, 8, and 12), sex, region (U.S./non-U.S.), BL number of incontinence episodes, and treatment by study visit interaction. hr = hours.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: OAB Wet	Vibegron 75 mg: OAB Wet	Tolterodine ER 4 mg: OAB Wet	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	372[31]	383[32]	286[33]	
Units: total incontinence episodes over 24 hr				
least squares mean (standard error)	-1.6 (± 0.15)	-2.3 (± 0.15)	-2.0 (± 0.16)	

Notes:

[31] - FAS-I. Only subjects with evaluable data were analyzed.

[32] - FAS-I. Only subjects with evaluable data were analyzed.

[33] - FAS-I. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: OAB Wet v Placebo: OAB Wet

Number of subjects included in analysis	755
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[34] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: OAB Wet v Placebo: OAB Wet
Number of subjects included in analysis	658
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074 [35]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[35] - Comparisons between tolterodine ER and placebo are considered descriptive.

Secondary: CFB at Week 12 in the Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB subjects

End point title	CFB at Week 12 in the Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB subjects

End point description:

The OAB-q LF is a validated patient-reported outcome. 8 questions of the OAB-q LF ask subjects how well they have coped with their bladder symptoms during the previous week, as a measure of quality of life (QoL). Each question has a response ranging from "not coping" (= 1) to "coping well" (= 6). These questions make up the coping scale. The raw score (sum of question scores [from 8 to 48]) is transformed to a unified score, from 0 to 100. Higher scores correspond to a higher QoL, and lower scores represent a lower QoL. CFB is calculated as the post-BL value minus the BL value. Covariates included in the MMRM were study visit (Weeks 2, 4, 8, and 12), sex, region (U.S./non-U.S.), OAB type (wet/dry), BL score, and treatment by study visit interaction. If < 50% of items were available, the subscore was regarded as missing; however, if ≥ 50% of items were available, the subscore included missing items imputed as the average of the remaining non-missing items for the subscore.

End point type	Secondary

End point timeframe:
Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	504[36]	512[37]	400[38]	
Units: units on a scale				
least squares mean (standard error)	12.9 (± 1.32)	16.5 (± 1.31)	16.0 (± 1.39)	

Notes:
[36] - FAS. Only subjects with evaluable data were analyzed.
[37] - FAS. Only subjects with evaluable data were analyzed.
[38] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	1016
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039 [39]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	6
Variability estimate	Standard error of the mean
Dispersion value	1.24

Notes:
[39] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	904
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [40]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	3.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	5.7
Variability estimate	Standard error of the mean
Dispersion value	1.32

Notes:

[40] - Comparisons between tolterodine ER and placebo are considered descriptive.

Secondary: CFB at Week 12 in the average volume voided per micturition in all OAB subjects

End point title	CFB at Week 12 in the average volume voided per micturition in all OAB subjects

End point description:

A micturition/void is defined as "Urinated in Toilet" as indicated on the PVD. The number of micturitions is defined as the number of times a subject voided in the toilet as indicated on the PVD. CFB is calculated as the post-BL value minus the BL value. Covariates included in the mixed model for repeated measures were study visit (Weeks 2, 4, 8, and 12), OAB type (wet/dry), sex, region (U.S./non-U.S.), BL volume (milliliters [mL]), and treatment by study visit interaction.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	478[41]	490[42]	375[43]	
Units: mL per micturition				
least squares mean (standard error)	2.2 (± 3.28)	23.5 (± 3.26)	15.5 (± 3.52)	

Notes:

[41] - FAS. Only subjects with evaluable data were analyzed.

[42] - FAS. Only subjects with evaluable data were analyzed.

[43] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	968
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [44]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	21.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	14.3
upper limit	28.1
Variability estimate	Standard error of the mean
Dispersion value	3.52

Notes:

[44] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [45]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.9
upper limit	20.7
Variability estimate	Standard error of the mean
Dispersion value	3.76

Notes:

[45] - Comparisons between tolterodine ER and placebo are considered descriptive.

Secondary: CFB at Week 12 in the Health-related Quality of Life (HRQL) Total Score from the OAB-q LF (1-week recall) in all OAB subjects

End point title	CFB at Week 12 in the Health-related Quality of Life (HRQL) Total Score from the OAB-q LF (1-week recall) in all OAB subjects

End point description:

The OAB-q LF is a validated patient-reported outcome. The 25 questions comprising the Coping, Concern, Sleep and Social Interaction subscales of the OAB-q LF ask subjects how much their symptoms have affected their life over the last week. Each question has a response ranging from "None of the time" (= 1) to "All of the time" (= 6). The raw score (sum of question scores for the 4 subscales [ranging from 25 to 150]) is transformed to a unified score, ranging from 0 to 100. Higher scores correspond to a higher quality of life, and lower scores represent a lower quality of life. CFB is calculated as the post-BL value minus the BL value. Covariates included in the mixed model for repeated measures were study visit (Weeks 2, 4, 8, and 12), sex, region (U.S./non-U.S.), OAB type (wet/dry), BL score, and treatment by study visit interaction. If < 50% of items were available, the subscore (SS) was regarded as missing; if ≥ 50% of items were available, the SS included missing items for SS.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	504[46]	512[47]	400[48]	
Units: units on a scale				
least squares mean (standard error)	10.8 (± 1.13)	14.6 (± 1.12)	13.7 (± 1.19)	

Notes:

[46] - FAS. Only subjects with evaluable data were analyzed.

[47] - FAS. Only subjects with evaluable data were analyzed.

[48] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	1016
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [49]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	5.8
Variability estimate	Standard error of the mean
Dispersion value	1.06

Notes:

[49] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	904
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0114
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	5.1
Variability estimate	Standard error of the mean
Dispersion value	1.13

Secondary: CFB at Week 12 in the Symptom Bother Score from the OAB-q LF (1-week recall) in all OAB subjects

End point title	CFB at Week 12 in the Symptom Bother Score from the OAB-q LF (1-week recall) in all OAB subjects

End point description:

The OAB-q LF is a validated patient-reported outcome. The first 8 questions of the OAB-q LF ask subjects how much they were bothered by their bladder symptoms during the previous week. Each question has a response ranging from "Not at all" (= 1) to "A very great deal" (= 6). These questions make up the symptom bother scale. The raw score (sum of question scores [from 8 to 48]) is transformed to a unified score, from 0 to 100. Higher scores correspond to the symptoms having a larger bother, and lower scores represent a lower amount of bother due to symptoms. CFB is calculated as the post-BL value minus the BL value. Covariates included in the MMRM were study visit (Weeks 2, 4, 8, and 12), sex, region (U.S./non-U.S.), OAB type (wet/dry), BL score, and treatment by study visit interaction. If < 50% of items were available, the SS was regarded as missing; if ≥ 50% of items were available, the SS included missing items imputed as the average of the remaining non-missing items for SS.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	504[50]	512[51]	400[52]	
Units: units on a scale				
least squares mean (standard error)	-12.8 (± 1.25)	-19.6 (± 1.24)	-17.4 (± 1.31)	

Notes:

[50] - FAS. Only subjects with evaluable data were analyzed.

[51] - FAS. Only subjects with evaluable data were analyzed.

[52] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	1016
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [53]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	-4.6

Variability estimate	Standard error of the mean
Dispersion value	1.17

Notes:

[53] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	904
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [54]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	-2.2
Variability estimate	Standard error of the mean
Dispersion value	1.25

Notes:

[54] - Comparisons between tolterodine ER and placebo are considered descriptive.

Secondary: Percentage of all OAB subjects with an average number of micturitions < 8 per 24 hours at Week 12

End point title	Percentage of all OAB subjects with an average number of micturitions < 8 per 24 hours at Week 12

End point description:

A micturition/void is defined as “Urinated in Toilet” as indicated on the PVD. The number of micturitions is defined as the number of times a subject voided in the toilet as indicated on the PVD. A subject was defined as having an average of < 8 daily micturitions if the arithmetic mean of the number of micturitions per day in the PVD was less than 8 . "Per 24 hours” corresponds to one Diary Day (i.e., time between when the subject got up for the day each morning and time the subject got up for the day the next morning as recorded in the PVD).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	520[55]	526[56]	417[57]	
Units: percentage of subjects				
number (not applicable)				
Unadjusted	28.7	40.1	35.0	
Adjusted for sex	24.8	37.2	31.6	

Notes:

[55] - FAS

[56] - FAS

[57] - FAS

Statistical analyses

Statistical analysis title	Difference in Percentage: Vibegron 75 mg:Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [58]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.7
upper limit	18.1

Notes:

[58] - The Cochran-Mantel-Haenszel (CMH) risk difference estimate was stratified by OAB type (wet/dry) and sex (female/male), with weights proposed by Greenland and Robins.

Statistical analysis title	Difference in Percentage: Tolterodine ER:Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	937
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0236 [59]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	12.8

Notes:

[59] - The Cochran-Mantel-Haenszel (CMH) risk difference estimate was stratified by OAB type (wet/dry) and sex (female/male), with weights proposed by Greenland and Robins.

Secondary: Percentage of OAB Wet subjects with at least a 50% reduction from Baseline in total incontinence episodes per 24 hours at Week 12

End point title	Percentage of OAB Wet subjects with at least a 50% reduction from Baseline in total incontinence episodes per 24 hours at Week 12

End point description:

Total incontinence is defined as having any reason for "Accidental Urine Leakage" and/or "Accidental Urine Leakage" checked, as indicated on the PVD. It is assumed that if the subject recorded a reason for leakage then the accidental urine leakage occurred. All events marked as having leakage, regardless of

cause, or where “Accidental Leakage” was checked. were used in the analysis. "Per 24 hours” corresponds to one Diary Day (i.e., time between when the subject got up for the day each morning and time the subject got up for the day the next morning as recorded in the PVD. The multiple imputation method was used for missing values.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: OAB Wet	Vibegron 75 mg: OAB Wet	Tolterodine ER 4 mg: OAB Wet	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	405[60]	403[61]	319[62]	
Units: percentage of subjects				
number (not applicable)				
Unadjusted	53.8	64.0	66.5	
Adjusted for sex	49.9	61.6	61.5	

Notes:

[60] - FAS-I. Only subjects with evaluable data were analyzed.

[61] - FAS-I. Only subjects with evaluable data were analyzed.

[62] - FAS-I. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	Difference in Percentage: Vibegron 75 mg:Placebo
Comparison groups	Placebo: OAB Wet v Vibegron 75 mg: OAB Wet
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [63]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	18.6

Notes:

[63] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex (female/male), with weights proposed by Greenland and Robins.

Statistical analysis title	Difference in Percentage: Tolterodine ER:Placebo
Comparison groups	Tolterodine ER 4 mg: OAB Wet v Placebo: OAB Wet
Number of subjects included in analysis	724
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022 [64]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	11.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	18.9

Notes:

[64] - The Cochran-Mantel-Haenszel risk difference estimate was stratified by sex (female/male), with weights proposed by Greenland and Robins.

Secondary: CFB at Week 12 in overall bladder symptoms based on Patient Global Impression of Severity (PGI-Severity) in all OAB subjects

End point title	CFB at Week 12 in overall bladder symptoms based on Patient Global Impression of Severity (PGI-Severity) in all OAB subjects

End point description:

The Patient Global Impression (PGI) questions are designed to assess a subject's overall impression of OAB. For the PGI-Severity score, subjects are asked to rate their OAB symptoms over the previous week with one of the following responses: 1 = none, 2 = mild, 3 = moderate, 4 = severe. CFB is calculated as the post-BL value minus the BL value. Covariates included in the mixed model for repeated measures were study visit (Weeks 2, 4, 8, and 12), OAB type (wet/dry), sex, region (U.S./non-U.S.), BL score, and treatment by study visit interaction.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	484[65]	494[66]	382[67]	
Units: units on a scale				
least squares mean (standard error)	-0.5 (± 0.04)	-0.8 (± 0.04)	-0.7 (± 0.04)	

Notes:

[65] - FAS. Only subjects with evaluable data were analyzed.

[66] - FAS. Only subjects with evaluable data were analyzed.

[67] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	978
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [68]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[68] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0055 [69]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[69] - Hypothesis testing was performed for vibegron minus placebo.

Secondary: CFB at Week 12 in overall control over bladder symptoms based on Patient Global Impression of Control (PGI-Control) in all OAB subjects

End point title	CFB at Week 12 in overall control over bladder symptoms based on Patient Global Impression of Control (PGI-Control) in all OAB subjects

End point description:

The Patient Global Impression (PGI) questions are designed to assess a subject's overall impression of OAB. For the PGI-Control score, subjects were asked to rate how much control they had over their OAB symptoms over the previous week with one of the following responses: 1 = complete control, 2 = a lot of control, 3 = some control, 4 = only a little control, 5 = no control. CFB is calculated as the post-BL value minus the BL value. Covariates included in the mixed model for repeated measures were study visit (Weeks 2, 4, 8, and 12), OAB type (wet/dry), sex, region (U.S./non-U.S.), BL score, and treatment by study visit interaction.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Placebo: Full Analysis Set	Vibegron 75 mg: Full Analysis Set	Tolterodine ER 4 mg: Full Analysis Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	484[70]	494[71]	382[72]	
Units: units on a scale				
least squares mean (standard error)	-0.7 (± 0.05)	-1.0 (± 0.05)	-0.9 (± 0.05)	

Notes:

[70] - FAS. Only subjects with evaluable data were analyzed.

[71] - FAS. Only subjects with evaluable data were analyzed.

[72] - FAS. Only subjects with evaluable data were analyzed.

Statistical analyses

Statistical analysis title	LS Mean Difference: Vibegron 75 mg minus Placebo
Comparison groups	Vibegron 75 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	978
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [73]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[73] - Hypothesis testing was performed for vibegron minus placebo.

Statistical analysis title	LS Mean Difference: Tolterodine ER minus Placebo
Comparison groups	Tolterodine ER 4 mg: Full Analysis Set v Placebo: Full Analysis Set
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [74]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:
[74] - Comparisons between tolterodine ER and placebo are considered descriptive.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from the time the subject provided informed consent to participate in the study at the Screening Visit until completion of the Follow-up Visit (up to Day 113 or Early Withdrawal plus 28 days)

Adverse event reporting additional description:

Treatment-emergent adverse events were collected in members of the Safety Set, comprised of all subjects who received at least 1 dose of study treatment. Subjects were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Vibegron 75 mg

Reporting group description:

Subjects received vibegron 75 milligrams (mg), orally, once daily for 12 weeks.

Reporting group title	Tolterodine ER 4 mg

Reporting group description:

Subjects received tolterodine extended release (ER) 4 mg, orally, once daily for 12 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo, orally, once daily for 12 weeks.

Serious adverse events	Vibegron 75 mg	Tolterodine ER 4 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 545 (1.47%)	10 / 430 (2.33%)	6 / 540 (1.11%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			

subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 545 (0.18%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendix disorder			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 545 (0.18%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 545 (0.00%)	1 / 430 (0.23%)	0 / 540 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 545 (0.00%)	0 / 430 (0.00%)	1 / 540 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Vibegron 75 mg	Tolterodine ER 4 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 545 (6.61%)	50 / 430 (11.63%)	38 / 540 (7.04%)
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	9 / 545 (1.65%)	28 / 430 (6.51%)	5 / 540 (0.93%)
occurrences (all)	9	29	5
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	27 / 545 (4.95%)	24 / 430 (5.58%)	33 / 540 (6.11%)
occurrences (all)	32	28	36

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2017	- Changes were made to description of contraception requirements and methods for female subject. - Plan to use a paper diary as backup was added.
01 November 2017	- Inclusion and exclusion criterion were updated. - A note that paper diaries may be used was added. - Clarification that pelvic examinations may be part of the physical examination and clarification that urinalysis was to be performed if there was a positive dipstick result was made. - Follicle-stimulating hormone was removed from clinical laboratory test performed. - The timing for collection of paper diaries (if used) was added. - References to the Week 2 time point as a visit were reworded to clarify that a study visit does not occur at Week 2. - "Tablet" or "capsule" descriptors were added. - Wording was added to indicate the study treatment should be swallowed whole. - Wording was added to require a witnessed dose at the clinic at Run-In and Baseline Visits. - Pharmacokinetic (PK) sub-study language was changed. - Dispense study medication was language was combined. - Clarified that tablet/capsule count was to be recorded in the interactive voice or web response system rather than case report form. - Added adverse events suggestive of cystitis or urinary tract infection and moved liver test values to end of list.
30 January 2018	- Addition of exploratory efficacy endpoints - Change of 5% in response efficacy endpoint - Change in statistical analysis from Last Observation Carried Forward to multiple imputation; subgroup analyses to include primary mixed model for repeated measure analysis model with a subgroup by treatment interaction term. - Updated Schedule of Activities and visit events - Updated language around timing of data collection for adverse events (AEs) and serious adverse events. - Changed days of screening compliance - Replaced "discontinued" with "interrupted" - Removed study medication rechallenge in subjects with a grade 3 or higher drug-related AE reported - Updated Patient Voiding Diary and Urine Volume Collection instructions, training, and description - Updated instructions on Reminders for Diary Collection - Updated Electronic Diary instructions and training - Deletion of data collection of food/meal intake prior to PK sampling - Updated Major Adverse Cardiac and Cerebrovascular Events language to match clinical adjudication committee Charter - Addition of time frame around pregnancy and infant outcome
12 February 2018	Minor typographical/formatting errors were corrected.

15 November 2018	- The key secondary efficacy endpoints were reordered, and key/other secondary efficacy endpoints were added and removed. - Exploratory endpoints were reordered and analysis timepoints were updated for some endpoints. - Exploratory endpoints were added and removed. - Removed language indicating that AEs from time of informed consent to first dose of study treatment should be recorded as medical history. - One objective/hypothesis was added, four key secondary objectives/hypotheses were deleted, and the objectives/hypotheses were reordered and renumbered accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported