SYNOPSIS

Title of the study:	Efficacy and Safety of 2mg/day of M100907 on Sleep Maintenance Insomnia with a sub-study of the effect of M100907 on stable Type II Diabetes Mellitus: a One Year, multi-center, randomized, double-blind, placebo-controlled study (LTE6673)
Investigator(s):	[redacted]
Study center(s):	This study was conducted in 238 active centers (sites that screened patients) in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, the Czech Republic, Germany, Hong Kong, India, Italy, Malaysia, Mexico, the Russian Federation, Singapore, South Africa, Spain, Turkey, United Kingdom, and the United States of America.
Publications (reference):	Not applicable
Study period:	
Date first patient enrolled:	17 April 2007
Date last patient completed:	11 March 2009
Phase of development:	3

Objectives:

Efficacy – Sleep maintenance insomnia

Primary objective:

- To demonstrate efficacy of M100907 2 mg/day in comparison to placebo as change from baseline to 3 months for Sleep Maintenance Insomnia using patient reported Wake After Sleep Onset (pr-WASO)

Secondary objectives:

- Key secondary
  - To assess efficacy of M100907 2 mg/day in comparison to placebo as change from baseline to 6 and 12 months for Sleep Maintenance Insomnia using patient reported Wake After Sleep Onset (pr-WASO)
  - To evaluate patient's daytime functioning on M100907 2 mg/day against placebo using change from baseline to 3 months in the "General Productivity" Domain score of the Functional Outcomes of Sleep Questionnaire (FOSQ)
- Other secondary objectives:
  - Sleep
    - To evaluate patient's daytime functioning on the 2 mg dose against placebo using change from baseline to 6, and 12 months in the "General Productivity" Domain score of the Functional Outcomes of Sleep Questionnaire (FOSQ)
    - To assess efficacy of M100907 2mg/day in comparison to placebo as change from baseline to 3, 6 and 12 months on other parameters of patient's sleep questionnaire.
  - Health Outcomes: To evaluate the effect on patient's ability to work at 3, 6 and 12 months of treatment, using the Work Limitation Questionnaire (WLQ). NOTE: The WLQ was only administered to patients who were currently working

Safety:

- To assess long-term clinical safety and tolerability of M100907 2 mg/day in comparison to placebo during the 12 months of treatment
- To evaluate subjective next morning residual effects associated with M100907 2 mg/day as compared to placebo at 3, 6, and 12 months of treatment
- To assess during the 1-week run-out period the effect on sleep (pr-WASO) following abrupt discontinuation after 12 months (or in case of premature discontinuation) of study treatment with M100907 2 mg/day in comparison to placebo

Subpopulation of type II diabetes mellitus with sleep maintenance insomnia:

Objectives:

- Efficacy:
  - To demonstrate improved glycemic control in patients with type II diabetes mellitus and sleep maintenance insomnia using change from baseline of HbA_{1C} at 6 and 12 months
  - To evaluate efficacy through a reduction in dose of medicine(s) required for adequate diabetes control after 6 and 12 months of treatment with M100907
- Safety in type II diabetes mellitus:
  - To establish the safety and tolerability of M100907 2 mg/day in patients with type II diabetes mellitus

This study was stopped prematurely by the Sponsor; therefore, the analysis (as defined in the statistical analysis plan) focused on a review of the safety profile based on the reported adverse events and results for the primary efficacy criterion. Limited appendices are included to support the data presented in this synopsis-style report.

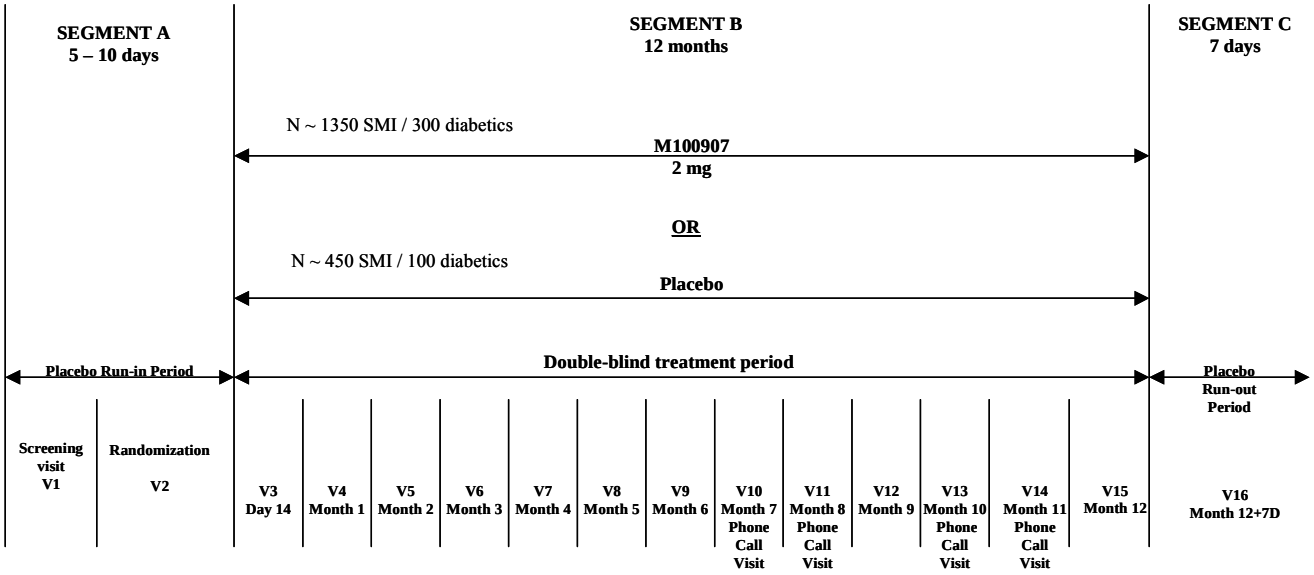
Methodology

This was an international, multicenter, randomized, 1-year (12 month) double-blind, placebo-controlled study with 2 parallel groups of patients with sleep maintenance insomnia.

After a single-blind placebo run-in period of up to 10 days, patients were to be centrally randomized to receive either volinanserin (international nonproprietary name for M100907) 2 mg/day or placebo in a 3:1 ratio using an interactive voice response system. The randomization was stratified by center and by type II diabetes status within each center. During the double-blind period, patients took 1 tablet of either placebo or volinanserin daily for 12 months. Patients were then to be followed for a single-blind placebo run-out period of 7 days. Patients withdrawing prematurely from the treatment period were to be followed for 7 days without placebo intake.

An external Data Monitoring Committee periodically reviewed patient safety data.

A summary of the study design is provided below.



Number of patients: Planned: 1800 (450 placebo, 1350 volinanserin; 400 with confirmed type II diabetes mellitus)

Randomized: 1847

Treated: 1841 (470 placebo, 1371 volinanserin)

Efficacy: 1798 (457 placebo, 1341 volinanserin)

Safety : 1841 (470 placebo, 1371 volinanserin)

Pharmacokinetics : Not applicable

Diagnosis and criteria for inclusion:

Patients ≥ 18 years of age with a diagnosis of primary insomnia based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition, with predominant complaints of difficulty maintaining sleep (nocturnal awakenings or early morning awakening) for at least 1 month preceding the study visit and having clinically significant distress or impairment in social, occupational, or other important areas of functioning.

In addition, based on the patient's information:

- The patient must have complained of at least 1 hour of wakefulness after sleep onset for at least 4 nights per week over the preceding month
- The patient must have spent at least 6.5 hours and not more than 9.0 hours in bed each night over the preceding 2 weeks
- The patient must have reported impact on daytime functioning associated with sleep maintenance insomnia as measured by question 3 of the Insomnia Severity Index at screening and randomization visits. To be included, the patient's answer should have been either 2 (=somewhat interfering), 3 (=much interfering), or 4 (=very much interfering)
- During the screening period, the patient must have reported
  - WASO ≥ 60 minutes on more than half of the nights
  - TST (total sleep time) ≤ 7 hours and ≥ 3 hours on the 3 worst nights
  - Excluding 1 night with the highest SOL (sleep onset latency) value, the mean SOL must have been ≤ 30 minutes

To be included in the diabetes substudy population, patients with sleep maintenance insomnia and an established medical diagnosis of type II diabetes mellitus must have been treated with either an oral hypoglycemic agent and/or insulin for at least 3 months prior to the screening visit (stable regimen for at least 1 month).

Investigational product: M100907 (international nonproprietary name: volinanserin) 2 mg tablet

Dose: 2 mg/day

Administration: oral, once daily around bedtime

Batch number: [redacted]

Duration of treatment: 12 months

Duration of observation: approximately 12 months and 2 weeks, including Segment A (run-in period, 5 to 10 days), Segment B (double-blind treatment period, 12 months), and Segment C (run-out period, 1 week).

Reference therapy: Placebo tablet (to match volinanserin)

Dose: 0 mg

Administration: Oral, once daily around bedtime

Batch number: [redacted]

Criteria for evaluation: The current report is a synopsis-style report; consequently, only safety results based on adverse events and results for the primary efficacy criterion are presented. Safety criteria were evaluated and analyzed using descriptive statistics.

Evaluation criteria as originally specified in the protocol are listed below.

Efficacy

Primary criterion: change in wake after sleep onset from baseline to 3 months measured by patient's sleep questionnaire (pr-WASO)

Key secondary criteria:

- Change in wake time after sleep onset measured by patient's sleep questionnaire (pr-WASO) from baseline to 6 months and 12 months
- Change in general productivity domain score from the Functional Outcomes of Sleep Questionnaire (FOSQ) from baseline to 3 months

Other secondary criteria

- Change in other sleep parameters from the patient's sleep questionnaire (number of nocturnal awakenings [pr-NAW], total sleep time [pr-TST], sleep onset latency [pr-SOL], patient-reported quality of sleep, and refreshing quality of sleep) and from the Patient Global Impression (PGI) questionnaire from baseline to 3, 6, and 12 months
- Change in other domains (not included in key secondary criteria) of the FOSQ from baseline to 3 months
- Change in all domains of the FOSQ (general productivity, activity level, vigilance, intimacy and sexual relationships, and social outcome) from baseline to 6 and 12 months
- Change in ability to perform work measured by the Work Limitation Questionnaire from baseline to 3, 6, and 12 months
- Change in mood evaluated by the Hospital Anxiety and Depression Scale from baseline to 3, 6, and 12 months

Safety

- Clinical safety throughout the study assessed by adverse events, standard laboratory tests, physical examinations, body weight, vital signs (supine and orthostatic blood pressure and pulse), 12-lead electrocardiograms
- Next morning residual effects (morning sleepiness, ability to concentrate in the morning) evaluated by change from baseline to 3, 6, and 12 months using patient's sleep questionnaire
- Rebound effect evaluated as change from baseline of pr-WASO and pr-TST at each timepoint of the run-out period (first day, mean of first 3 days, mean of the run-out period)
- Daily assessment of withdrawal effect during the run-out period using the Physician Withdrawal Checklist

Criteria for the diabetes mellitus type II substudy

- Change in HbA_{1C} (glycosylated hemoglobin) from baseline to 6 and 12 months
- Reduction in dose of medicine(s) required for adequate diabetic control from baseline to 6 and 12 months

Statistical methods:

Based on the absence of a demonstration of efficacy in the recently completed Phase 3 LTE6672 study, the Sponsor has decided to discontinue the volinanserin development program in sleep maintenance insomnia. Accordingly, this ongoing study was prematurely terminated. Analyses specified in the Statistical Analysis Plan focused on patient disposition, demography, extent of exposure, the primary criterion, and adverse events.

Demographic characteristics were summarized on the randomized population. Continuous data were summarized using the number of available data, mean, standard deviation (SD), median, and minimum and maximum for each treatment group. Categorical and ordinal data were summarized using counts and percentages of patients in each treatment group.

Efficacy

The primary efficacy analysis, the comparison of the change from baseline in the mean of pr-WASO between volinanserin and placebo after 3 months of double-blind treatment, was performed on the intent-to-treat population, defined as all randomized patients who received at least 1 dose of double-blind study medication and provided baseline and postbaseline pr-WASO data. A mixed-effect model with repeated measures (MMRM), assuming a missing-at-random mechanism, was used in the analysis. The model included the fixed categorical effects of treatment (2 levels, volinanserin and placebo), visit (13 levels: Weeks 1 to 2, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12), and treatment-by-visit interaction as well as continuous fixed covariates of centered baseline mean WASO (ie, baseline mean pr-WASO after centered baseline individual values on the grand mean baseline), with subject as a random effect included in the error term.

The model provides the baseline-adjusted least-squares mean (LS-mean) estimate at Month 3 by treatment group, as well as the difference of the estimate versus placebo, with the corresponding standard errors, degrees of freedom, Student t-test statistics, and associated 95% confidence intervals.

No other efficacy analyses were performed. No pharmacokinetic or pharmacogenetic data were analyzed.

Safety

Safety and extent of exposure analyses were summarized on the all-treated population, defined as all randomized patients exposed to study treatment regardless of the amount of treatment administered. Safety analyses focused on treatment-emergent adverse events (TEAEs), defined as events that developed, worsened, or became serious during the on-treatment period (from the 1st double-blind study drug intake up to 5 days [5 half-lives] after the last double-blind study drug intake). Frequency distributions of TEAEs are provided by system organ class and preferred term and by system organ class, high-level group term, high-level term, and preferred term and include TEAEs leading to treatment discontinuation. Adverse events were coded before study unblinding using the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1

Summary:

Patient disposition

A total of 4020 patients were enrolled (screened) in the study and 1869 patients were randomized. Twenty-two randomized patients were excluded from all analyses: 10 patients were enrolled more than once (leading to 12 multiple randomizations), and 10 patients were enrolled at a study site that was closed due to Good Clinical Practice (GCP) noncompliance and potential scientific misconduct. The most common reason for nonrandomization was not meeting the inclusion/exclusion criteria (48.0%). The table below provides a summary of the screened population.

Summary of screened population

	Screened patients (N=4020)
Randomized patients including multiple randomizations	1869 (46.5%)
Patients excluded from all analyses due to multiple randomizations	12 (0.3%)
Patients excluded from analysis due to site closure	10 (0.2%)
Randomized patients	1847 (45.9%)
Non-randomized patients	2151 (53.5%)
Non-randomized and exposed patients	0
Reason for non-randomization	
Inclusion/exclusion criteria not respected	1928 (48.0%)
Adverse event	17 (0.4%)
Withdrawal of consent	168 (4.2%)
Lost to follow-up	31 (0.8%)
Other	30 (0.7%)

Note: % calculated using the number of screened patients as denominator.
Multiple reasons for non-randomization are possible

A total of 1841 patients were exposed to at least 1 dose of placebo or volinanserin treatment. A total of 353 patients completed the study treatment period; the primary reason for treatment discontinuation was study termination by the Sponsor. The rate of discontinuation was similar in both treatment groups (83.7% in the placebo group, 79.9% in the volinanserin group). A summary of patient disposition is provided in the table below.

Summary of patient disposition at end of double-blind treatment number (%) - randomized population

	Placebo (N=472)	Volinanserin 2mg/day (N=1375)
Exposed patients	470 (99.6%)	1371 (99.7%)
Completed study treatment period	77 (16.3%)	276 (20.1%)
Discontinued study treatment period	395 (83.7%)	1099 (79.9%)
Reason for treatment discontinuation		
Lack of efficacy	82 (17.4%)	199 (14.5%)
Adverse event	28 (5.9%)	91 (6.6%)
Subject's request	26 (5.5%)	77 (5.6%)
Subject lost to follow-up	16 (3.4%)	47 (3.4%)
Other reason	243 (51.5%)	685 (49.8%)

Note: % calculated using the number of randomized patients as denominator.

Study populations

Populations analyzed for the study are presented below. Of patients in the randomized population, 6 patients (2 randomized to placebo and 4 to volinanserin) did not receive any study treatment; of patients who received study treatment, 43 patients (13 randomized to placebo and 30 to volinanserin) had no baseline or postbaseline pr-WASO assessments.

Summary of populations - randomized population

	Placebo	Volinanserin 2mg/day	All
Randomized population	472 (100%)	1375 (100%)	1847 (100%)
All treated population	470 (99.6%)	1371 (99.7%)	1841 (99.7%)
ITT Population	457 (96.8%)	1341 (97.5%)	1798 (97.3%)

Note: % calculated using the number of randomized patients as denominator.
ITT : Intent to Treat

Demographics and other baseline characteristics

Demography

Baseline characteristics were similar across treatment groups (see table below).

Summary of demographic characteristics at baseline - randomized population

	Placebo (N=472)	Volinanserin 2mg/day (N=1375)	All (N=1847)
Gender, n(%)			
Number	472	1375	1847
Male	186 (39.4%)	595 (43.3%)	781 (42.3%)
Female	286 (60.6%)	780 (56.7%)	1066 (57.7%)
Race, n(%)			
Number	472	1375	1847
Asian / oriental	17 (3.6%)	64 (4.7%)	81 (4.4%)
Black	36 (7.6%)	82 (6.0%)	118 (6.4%)
Caucasian / white	415 (87.9%)	1225 (89.1%)	1640 (88.8%)
Other	4 (0.8%)	4 (0.3%)	8 (0.4%)
Age(years)			
Number	472	1375	1847
Mean (SD)	51.46 (12.82)	52.33 (13.21)	52.11 (13.12)
Median	51.00	53.00	52.00
Q1:Q3	43.00 : 60.00	43.00 : 62.00	43.00 : 61.00
Min : Max	19.0 : 88.0	19.0 : 91.0	19.0 : 91.0
Age Group, n(%)			
Number	472	1375	1847
[18-45[years	137 (29.0%)	378 (27.5%)	515 (27.9%)
[45-65[years	255 (54.0%)	742 (54.0%)	997 (54.0%)
>= 65 years	80 (16.9%)	255 (18.5%)	335 (18.1%)
Weight (kg)			
Number	471	1375	1846
Mean (SD)	74.2 (14.8)	74.6 (14.2)	74.5 (14.4)
Median	73.0	74.0	74.0
Q1:Q3	64.0 : 83.4	64.0 : 83.8	64.0 : 83.7
Min : Max	36 : 126	34 : 129	34 : 129
BMI (kg/m^2)			
Number	471	1375	1846
Mean (SD)	26.2 (3.7)	26.2 (3.7)	26.2 (3.7)
Median	26.2	26.0	26.1
Q1:Q3	23.4 : 29.1	23.5 : 29.0	23.5 : 29.0
Min : Max	17 : 34	13 : 35	13 : 35

Note: Number corresponds to the count of patients with non missing data used for the calculation of the percentage.

Disease characteristics at baseline

At baseline, the mean time to first diagnosis of insomnia was approximately 8 years in both treatment groups. Approximately 50% of patients had a first insomnia diagnosis more than 5 years prior to their participation in the study.

Summary of primary insomnia diagnosis - randomized population

	Placebo (N=472)	Volinanserin 2mg/day (N=1375)	All (N=1847)
Time from first diagnosis (years)			
Number	468	1365	1833
Mean (SD)	7.640 (9.191)	8.303 (9.766)	8.134 (9.624)
Median	4.274	4.967	4.830
Q1:Q3	1.316 : 10.534	1.466 : 10.852	1.444 : 10.734
Min : Max	0.11 : 68.44	0.02 : 61.97	0.02 : 68.44
Distribution, n (%)			
Number	468	1365	1833
[0 to 0.5]	58 (12.4%)	138 (10.1%)	196 (10.7%)
]0.5 to 1]	38 (8.1%)	132 (9.7%)	170 (9.3%)
]1 to 5]	151 (32.3%)	402 (29.5%)	553 (30.2%)
]5 to 10]	89 (19.0%)	274 (20.1%)	363 (19.8%)
>10	132 (28.2%)	419 (30.7%)	551 (30.1%)

Note: Number corresponds to the count of patients with non missing data used for the calculation of the percentage.

Efficacy parameters at baseline

Descriptive statistics for pr-WASO at baseline are provided in the table below.

Summary of patient-reported wake after sleep onset at baseline - randomized population

	Placebo (N=472)	Volinanserin 2mg/day (N=1375)	All (N=1847)
Patient reported WASO (min:sec)			
Number	471	1372	1843
Mean (SD)	100:56 (49:05)	103:35 (60:43)	102:55 (57:58)
Median	90:00	90:00	90:00
Q1:Q3	70:00 :120:00	70:00 :120:00	70:00 :120:00
Min : Max	2:00 :500:00	1:00 :935:00	1:00 :935:00

Note: pr: patient reported, WASO: Wake time after sleep onset
Number corresponds to the count of patients with non missing data.

Efficacy results

The primary efficacy analysis showed a modest effect of volinanserin 2 mg/day against placebo on the change from baseline of pr-WASO after 3 months of treatment (LS mean change from baseline of -35:40 min:sec for the placebo group and 43:29 min:sec for the volinanserin group, LS mean difference of -7:49 min:sec, p-value=0.0036).

Summary of patient-reported wake after sleep onset (min : sec) change from baseline at month 3 (mixed-effect model with repeated measures) – intent-to-treat population

	Placebo (N=457)	Volinanserin 2mg/day (N=1341)
Number	457	1341
Baseline		
Mean (SD)	101:00 (49:12)	103:40 (61:01)
Median	90:00	90:00
Q1 : Q3	70:00 : 120:00	70:00 : 120:00
Min : Max	2:00 : 500:00	1:00 : 935:00
Change from baseline at month 3 (V6)		
LS Mean (SEM)	-35:40 (2:19)	-43:29 (1:21)
LS Mean Difference from placebo (SEM)		-7:49 (2:41)
95% Confidence Interval		(-13:05 to -2:33)
p-value vs. Placebo		0.0036

Note: pr-WASO: patient reported wake time after sleep onset
Number refers to patients with baseline and post-baseline values
Estimations and p-value based on a Repeated Measurement Model with centered baseline as covariate

Safety results

Extent of exposure

The mean treatment duration was approximately 175 days for the placebo group and 182 days for the volinanserin group.

Summary of exposure to double-blind treatment – all-treated population

	Placebo (N=470)	Volinanserin 2mg/day (N=1371)
Extent of exposure (days)		
Number	470	1371
Mean (SD)	174.7 (121.9)	182.0 (127.8)
Median	148.0	155.0
Q1:Q3	61.0 : 289.0	60.0 : 328.0
Min : Max	1 : 372	1 : 394
Number (%) of patients by interval of time		
]0-2] weeks	16 (3.4%)	64 (4.7%)
]2-4] weeks	32 (6.8%)	87 (6.3%)
]4-8] weeks	51 (10.9%)	158 (11.5%)
]8-13] weeks	66 (14.0%)	178 (13.0%)
]13-26] weeks	110 (23.4%)	276 (20.1%)
]26-39] weeks	70 (14.9%)	183 (13.3%)
]39-52] weeks	120 (25.5%)	392 (28.6%)
> 52 weeks	5 (1.1%)	33 (2.4%)

Note: Number corresponds to the count of patients with non missing data used for the calculation.

Summary of adverse events

More than half of the patients experienced TEAEs (53.2% in the placebo group versus 56.0% in the volinanserin group). The percentage of treatment-emergent serious adverse events was similar in the 2 treatment groups (2.3% in the placebo group versus 2.9% in the volinanserin group). The percentage of patients who discontinued treatment due to TEAEs was 5.7% in the placebo group versus 6.6% in the volinanserin group. The safety profile is presented in the table below.

Overview of safety profile: number (%) of patients – all-treated population

	Placebo (N=470)	Volinanserin 2mg/day (N=1371)
Patients with any TEAE (including SAEs)	250 (53.2%)	768 (56.0%)
Patients with any serious TEAEs (including SAEs leading to death)	11 (2.3%)	40 (2.9%)
Deaths	0	1 (<0.1%)
Patients permanently discontinued treatment due to TEAE	27 (5.7%)	90 (6.6%)

Note: TEAE: Treatment emergent adverse event. SAE: serious adverse event.
Adverse events coded in MedDRA version 11.1

Summary of treatment-emergent adverse events

Treatment-emergent adverse events reported during the study are presented in the table below by treatment group. No patterns of occurrence of TEAEs were observed, and frequencies of TEAEs were similar in both treatment groups. The most frequently occurring TEAEs were reported in the infections and infestations, nervous system disorders, and gastrointestinal disorders system organ classes; headache was the most frequently reported TEAE, reported by 8.9% of patients in the placebo group and 10.3% in the volinanserin group. There were 4 occurrences of diverticulitis, one of the adverse events of special interest specified in the protocol, 1 in the placebo group and 3 in the volinanserin group. All were mild or moderate. All patients received antibiotics as corrective treatment and recovered by the end of the study.

In addition, 2 nonserious adverse events (hypertension in the volinanserin group and drowsiness in the placebo group) were collected after the database was locked. Both adverse events were mild.

Number (%) of patients experiencing treatment-emergent adverse events by primary system organ class and preferred term – all-treated population

- Primary system organ class by Preferred term	Placebo (N=470)	Volinanserin 2mg/day (N=1371)
Any TEAE	250 (53.2%)	768 (56.0%)
Infections and infestations	95 (20.2%)	315 (23.0%)
Nasopharyngitis	24 (5.1%)	66 (4.8%)
Upper respiratory tract infection	14 (3.0%)	61 (4.4%)
Influenza	21 (4.5%)	55 (4.0%)
Sinusitis	9 (1.9%)	26 (1.9%)
Bronchitis	10 (2.1%)	20 (1.5%)
Urinary tract infection	8 (1.7%)	18 (1.3%)
Gastroenteritis	5 (1.1%)	18 (1.3%)
Pharyngitis	3 (0.6%)	10 (0.7%)
Tooth infection	1 (0.2%)	10 (0.7%)
Tooth abscess	3 (0.6%)	9 (0.7%)
Respiratory tract infection	1 (0.2%)	6 (0.4%)
Gastroenteritis viral	3 (0.6%)	5 (0.4%)
Otitis media	0	5 (0.4%)

Oral herpes	2	(0.4%)	4	(0.3%)
Rhinitis	2	(0.4%)	4	(0.3%)
Cystitis	1	(0.2%)	4	(0.3%)
Ear infection	1	(0.2%)	4	(0.3%)
Laryngitis	1	(0.2%)	4	(0.3%)
Lower respiratory tract infection	1	(0.2%)	4	(0.3%)
Pharyngotonsillitis	1	(0.2%)	4	(0.3%)
Respiratory tract infection viral	1	(0.2%)	4	(0.3%)
Fungal infection	0		4	(0.3%)
Diverticulitis	1	(0.2%)	3	(0.2%)
Herpes zoster	1	(0.2%)	3	(0.2%)
Pneumonia	1	(0.2%)	3	(0.2%)
Acute sinusitis	0		3	(0.2%)
Hordeolum	0		3	(0.2%)
Pharyngitis streptococcal	0		3	(0.2%)
Oral candidiasis	0		2	(0.1%)
Sinobronchitis	0		2	(0.1%)
Skin infection	0		2	(0.1%)
Tonsillitis	0		2	(0.1%)
Viral infection	0		2	(0.1%)
Viral upper respiratory tract infection	0		2	(0.1%)
Helicobacter infection	1	(0.2%)	1	(<0.1%)
Tracheitis	1	(0.2%)	1	(<0.1%)
Abscess limb	0		1	(<0.1%)
Acarodermatitis	0		1	(<0.1%)
Acute tonsillitis	0		1	(<0.1%)
Amoebic dysentery	0		1	(<0.1%)
Bacterial tracheitis	0		1	(<0.1%)
Cervicitis	0		1	(<0.1%)
Escherichia infection	0		1	(<0.1%)
Furuncle	0		1	(<0.1%)
Gastroenteritis salmonella	0		1	(<0.1%)
Gastrointestinal infection	0		1	(<0.1%)
Genital infection	0		1	(<0.1%)
Helicobacter gastritis	0		1	(<0.1%)
Impetigo	0		1	(<0.1%)
Infected cyst	0		1	(<0.1%)
Intervertebral discitis	0		1	(<0.1%)
Labyrinthitis	0		1	(<0.1%)
Localised infection	0		1	(<0.1%)
Lyme disease	0		1	(<0.1%)
Onychomycosis	0		1	(<0.1%)
Orchitis	0		1	(<0.1%)
Otitis externa	0		1	(<0.1%)
Otitis media chronic	0		1	(<0.1%)
Paronychia	0		1	(<0.1%)
Tinea pedis	0		1	(<0.1%)
Tracheobronchitis	0		1	(<0.1%)

Vulvovaginal candidiasis	0	1 (<0.1%)
Otitis media acute	1 (0.2%)	0
Post procedural infection	1 (0.2%)	0
Pulpitis dental	1 (0.2%)	0
Sialoadenitis	1 (0.2%)	0
Vulvovaginal mycotic infection	1 (0.2%)	0
Nervous system disorders	71 (15.1%)	256 (18.7%)
Headache	42 (8.9%)	141 (10.3%)
Somnolence	11 (2.3%)	44 (3.2%)
Dizziness	7 (1.5%)	42 (3.1%)
Migraine	5 (1.1%)	14 (1.0%)
Disturbance in attention	1 (0.2%)	11 (0.8%)
Lethargy	1 (0.2%)	11 (0.8%)
Paraesthesia	2 (0.4%)	7 (0.5%)
Tremor	0	7 (0.5%)
Dysgeusia	2 (0.4%)	4 (0.3%)
Hypoaesthesia	1 (0.2%)	4 (0.3%)
Memory impairment	1 (0.2%)	4 (0.3%)
Sciatica	1 (0.2%)	4 (0.3%)
Tension headache	1 (0.2%)	4 (0.3%)
Sedation	0	3 (0.2%)
Sinus headache	0	3 (0.2%)
Balance disorder	1 (0.2%)	2 (0.1%)
Restless legs syndrome	1 (0.2%)	2 (0.1%)
Cognitive disorder	0	2 (0.1%)
Dizziness postural	0	2 (0.1%)
Dysarthria	0	2 (0.1%)
Carpal tunnel syndrome	1 (0.2%)	1 (<0.1%)
Ageusia	0	1 (<0.1%)
Amnesia	0	1 (<0.1%)
Burning sensation	0	1 (<0.1%)
Carotid artery stenosis	0	1 (<0.1%)
Circadian rhythm sleep disorder	0	1 (<0.1%)
Coordination abnormal	0	1 (<0.1%)
Encephalopathy	0	1 (<0.1%)
Facial palsy	0	1 (<0.1%)
Hyperaesthesia	0	1 (<0.1%)
Intercostal neuralgia	0	1 (<0.1%)
Migraine with aura	0	1 (<0.1%)
Nerve compression	0	1 (<0.1%)
Subarachnoid haemorrhage	0	1 (<0.1%)
Trigeminal neuralgia	0	1 (<0.1%)
Cerebral infarction	1 (0.2%)	0
Dysaesthesia	1 (0.2%)	0
Petit mal epilepsy	1 (0.2%)	0
Gastrointestinal disorders	60 (12.8%)	200 (14.6%)

Diarrhoea	13	(2.8%)	42	(3.1%)
Nausea	9	(1.9%)	37	(2.7%)
Constipation	4	(0.9%)	26	(1.9%)
Dry mouth	10	(2.1%)	25	(1.8%)
Dyspepsia	5	(1.1%)	16	(1.2%)
Vomiting	6	(1.3%)	15	(1.1%)
Toothache	1	(0.2%)	13	(0.9%)
Abdominal pain upper	5	(1.1%)	12	(0.9%)
Gastritis	5	(1.1%)	10	(0.7%)
Abdominal pain	4	(0.9%)	10	(0.7%)
Gastrooesophageal reflux disease	1	(0.2%)	9	(0.7%)
Flatulence	1	(0.2%)	5	(0.4%)
Dental caries	1	(0.2%)	3	(0.2%)
Food poisoning	1	(0.2%)	3	(0.2%)
Inguinal hernia	1	(0.2%)	3	(0.2%)
Haemorrhoids	0		3	(0.2%)
Irritable bowel syndrome	0		3	(0.2%)
Stomach discomfort	0		3	(0.2%)
Abdominal discomfort	2	(0.4%)	2	(0.1%)
Abdominal distension	1	(0.2%)	2	(0.1%)
Abdominal pain lower	0		2	(0.1%)
Mouth ulceration	1	(0.2%)	1	(<0.1%)
Abdominal tenderness	0		1	(<0.1%)
Aphthous stomatitis	0		1	(<0.1%)
Breath odour	0		1	(<0.1%)
Colitis ulcerative	0		1	(<0.1%)
Colonic polyp	0		1	(<0.1%)
Diverticulum	0		1	(<0.1%)
Duodenitis	0		1	(<0.1%)
Gastric ulcer	0		1	(<0.1%)
Gastric ulcer haemorrhage	0		1	(<0.1%)
Haematemesis	0		1	(<0.1%)
Hypoaesthesia oral	0		1	(<0.1%)
Odynophagia	0		1	(<0.1%)
Oesophageal pain	0		1	(<0.1%)
Peptic ulcer	0		1	(<0.1%)
Periodontitis	0		1	(<0.1%)
Rectal haemorrhage	0		1	(<0.1%)
Reflux oesophagitis	0		1	(<0.1%)
Salivary hypersecretion	0		1	(<0.1%)
Stomatitis	0		1	(<0.1%)
Cheilitis	1	(0.2%)	0	
Dental discomfort	1	(0.2%)	0	
Frequent bowel movements	1	(0.2%)	0	
Glossodynia	1	(0.2%)	0	
Lip dry	1	(0.2%)	0	
Tongue cyst	1	(0.2%)	0	
Tongue ulceration	1	(0.2%)	0	

Umbilical hernia	1	(0.2%)	0	
Musculoskeletal and connective tissue disorders	39	(8.3%)	158	(11.5%)
Arthralgia	8	(1.7%)	32	(2.3%)
Back pain	11	(2.3%)	31	(2.3%)
Pain in extremity	5	(1.1%)	23	(1.7%)
Myalgia	5	(1.1%)	12	(0.9%)
Osteoarthritis	2	(0.4%)	9	(0.7%)
Musculoskeletal pain	2	(0.4%)	8	(0.6%)
Muscle spasms	3	(0.6%)	7	(0.5%)
Neck pain	3	(0.6%)	6	(0.4%)
Musculoskeletal chest pain	0		5	(0.4%)
Pain in jaw	0		5	(0.4%)
Intervertebral disc protrusion	2	(0.4%)	4	(0.3%)
Arthritis	1	(0.2%)	4	(0.3%)
Musculoskeletal stiffness	0		4	(0.3%)
Tendonitis	0		4	(0.3%)
Spinal osteoarthritis	0		3	(0.2%)
Bursitis	0		2	(0.1%)
Exostosis	0		2	(0.1%)
Fibromyalgia	0		2	(0.1%)
Foot deformity	0		2	(0.1%)
Groin pain	0		2	(0.1%)
Joint swelling	0		2	(0.1%)
Muscle contracture	0		2	(0.1%)
Osteoporosis	0		2	(0.1%)
Rotator cuff syndrome	0		2	(0.1%)
Sensation of heaviness	0		2	(0.1%)
Synovial cyst	0		2	(0.1%)
Flank pain	2	(0.4%)	1	(<0.1%)
Rheumatoid arthritis	2	(0.4%)	1	(<0.1%)
Joint stiffness	1	(0.2%)	1	(<0.1%)
Limb discomfort	1	(0.2%)	1	(<0.1%)
Bunion	0		1	(<0.1%)
Chondritis	0		1	(<0.1%)
Costochondritis	0		1	(<0.1%)
Intervertebral disc degeneration	0		1	(<0.1%)
Joint effusion	0		1	(<0.1%)
Loose body in joint	0		1	(<0.1%)
Muscle tightness	0		1	(<0.1%)
Muscular weakness	0		1	(<0.1%)
Nodule on extremity	0		1	(<0.1%)
Torticollis	2	(0.4%)	0	
Musculoskeletal discomfort	1	(0.2%)	0	
Osteopenia	1	(0.2%)	0	
Trismus	1	(0.2%)	0	
Injury, poisoning and procedural complications	37	(7.9%)	102	(7.4%)

Accidental overdose	11	(2.3%)	17	(1.2%)
Fall	6	(1.3%)	16	(1.2%)
Contusion	2	(0.4%)	12	(0.9%)
Road traffic accident	2	(0.4%)	8	(0.6%)
Muscle strain	1	(0.2%)	8	(0.6%)
Intentional overdose	0		6	(0.4%)
Back injury	2	(0.4%)	5	(0.4%)
Procedural pain	2	(0.4%)	5	(0.4%)
Joint sprain	2	(0.4%)	4	(0.3%)
Tooth fracture	1	(0.2%)	4	(0.3%)
Skin laceration	1	(0.2%)	3	(0.2%)
Excoriation	0		3	(0.2%)
Injury	0		3	(0.2%)
Limb injury	0		3	(0.2%)
Animal bite	1	(0.2%)	2	(0.1%)
Meniscus lesion	1	(0.2%)	2	(0.1%)
Tendon rupture	1	(0.2%)	2	(0.1%)
Ankle fracture	0		2	(0.1%)
Arthropod bite	0		2	(0.1%)
Epicondylitis	0		2	(0.1%)
Foot fracture	0		2	(0.1%)
Hand fracture	0		2	(0.1%)
Joint dislocation	0		2	(0.1%)
Post-traumatic pain	2	(0.4%)	1	(<0.1%)
Soft tissue injury	2	(0.4%)	1	(<0.1%)
Concussion	1	(0.2%)	1	(<0.1%)
Laceration	1	(0.2%)	1	(<0.1%)
Rib fracture	1	(0.2%)	1	(<0.1%)
Thermal burn	1	(0.2%)	1	(<0.1%)
Wrist fracture	1	(0.2%)	1	(<0.1%)
Accident	0		1	(<0.1%)
Accident at work	0		1	(<0.1%)
Burn oesophageal	0		1	(<0.1%)
Cartilage injury	0		1	(<0.1%)
Failure of implant	0		1	(<0.1%)
Joint injury	0		1	(<0.1%)
Multiple injuries	0		1	(<0.1%)
Neck injury	0		1	(<0.1%)
Overdose	0		1	(<0.1%)
Patella fracture	0		1	(<0.1%)
Pneumothorax traumatic	0		1	(<0.1%)
Post procedural complication	0		1	(<0.1%)
Renal injury	0		1	(<0.1%)
Splenic rupture	0		1	(<0.1%)
Synovial rupture	0		1	(<0.1%)
Tendon injury	0		1	(<0.1%)
Traumatic fracture	0		1	(<0.1%)
Bursa injury	1	(0.2%)	0	

Ligament injury	1	(0.2%)	0	
Nerve injury	1	(0.2%)	0	
Upper limb fracture	1	(0.2%)	0	
Psychiatric disorders	25	(5.3%)	89	(6.5%)
Anxiety	5	(1.1%)	29	(2.1%)
Insomnia	3	(0.6%)	16	(1.2%)
Depression	5	(1.1%)	11	(0.8%)
Abnormal dreams	4	(0.9%)	7	(0.5%)
Stress	1	(0.2%)	4	(0.3%)
Early morning awakening	0		3	(0.2%)
Nightmare	0		3	(0.2%)
Depressed mood	4	(0.9%)	2	(0.1%)
Initial insomnia	1	(0.2%)	2	(0.1%)
Adjustment disorder	0		2	(0.1%)
Agitation	0		2	(0.1%)
Nervousness	0		2	(0.1%)
Confusional state	2	(0.4%)	1	(<0.1%)
Euphoric mood	1	(0.2%)	1	(<0.1%)
Adjustment disorder with depressed mood	0		1	(<0.1%)
Affect lability	0		1	(<0.1%)
Anxiety disorder	0		1	(<0.1%)
Apathy	0		1	(<0.1%)
Bipolar i disorder	0		1	(<0.1%)
Burnout syndrome	0		1	(<0.1%)
Depersonalisation	0		1	(<0.1%)
Derealisation	0		1	(<0.1%)
Disturbance in sexual arousal	0		1	(<0.1%)
Illusion	0		1	(<0.1%)
Middle insomnia	0		1	(<0.1%)
Mood swings	0		1	(<0.1%)
Negative thoughts	0		1	(<0.1%)
Panic attack	0		1	(<0.1%)
Parasomnia	0		1	(<0.1%)
Restlessness	0		1	(<0.1%)
Sleep disorder	0		1	(<0.1%)
Withdrawal syndrome	0		1	(<0.1%)
Acute stress disorder	2	(0.4%)	0	
Libido decreased	1	(0.2%)	0	
General disorders and administration site conditions	29	(6.2%)	86	(6.3%)
Fatigue	10	(2.1%)	28	(2.0%)
Irritability	2	(0.4%)	8	(0.6%)
Asthenia	0		8	(0.6%)
Pyrexia	2	(0.4%)	7	(0.5%)
Influenza like illness	2	(0.4%)	6	(0.4%)
Chest pain	3	(0.6%)	5	(0.4%)
Pain	2	(0.4%)	5	(0.4%)

Malaise	0		5	(0.4%)
Non-cardiac chest pain	1	(0.2%)	4	(0.3%)
Oedema peripheral	4	(0.9%)	3	(0.2%)
Chest discomfort	3	(0.6%)	2	(0.1%)
Sluggishness	1	(0.2%)	2	(0.1%)
Inflammation	0		2	(0.1%)
Thirst	1	(0.2%)	1	(<0.1%)
Discomfort	0		1	(<0.1%)
Energy increased	0		1	(<0.1%)
Facial pain	0		1	(<0.1%)
Feeling abnormal	0		1	(<0.1%)
Feeling jittery	0		1	(<0.1%)
Gait disturbance	0		1	(<0.1%)
Hangover	0		1	(<0.1%)
Hernia	0		1	(<0.1%)
Nodule	0		1	(<0.1%)
Oedema	0		1	(<0.1%)
Sensation of foreign body	0		1	(<0.1%)
Respiratory, thoracic and mediastinal disorders	34	(7.2%)	62	(4.5%)
Cough	9	(1.9%)	19	(1.4%)
Oropharyngeal pain	13	(2.8%)	16	(1.2%)
Nasal congestion	2	(0.4%)	5	(0.4%)
Sinus congestion	2	(0.4%)	5	(0.4%)
Asthma	1	(0.2%)	5	(0.4%)
Dyspnoea	2	(0.4%)	3	(0.2%)
Dysphonia	1	(0.2%)	3	(0.2%)
Sleep apnoea syndrome	1	(0.2%)	3	(0.2%)
Productive cough	1	(0.2%)	2	(0.1%)
Snoring	1	(0.2%)	2	(0.1%)
Rhinitis allergic	1	(0.2%)	1	(<0.1%)
Rhinorrhoea	1	(0.2%)	1	(<0.1%)
Emphysema	0		1	(<0.1%)
Epistaxis	0		1	(<0.1%)
Nasal septum deviation	0		1	(<0.1%)
Pneumonitis	0		1	(<0.1%)
Wheezing	0		1	(<0.1%)
Pulmonary congestion	2	(0.4%)	0	
Interstitial lung disease	1	(0.2%)	0	
Postnasal drip	1	(0.2%)	0	
Pulmonary oedema	1	(0.2%)	0	
Skin and subcutaneous tissue disorders	21	(4.5%)	55	(4.0%)
Rash	4	(0.9%)	9	(0.7%)
Pruritus	1	(0.2%)	9	(0.7%)
Hyperhidrosis	3	(0.6%)	6	(0.4%)
Urticaria	1	(0.2%)	5	(0.4%)
Acne	1	(0.2%)	3	(0.2%)

Skin irritation	0		3	(0.2%)
Alopecia	1	(0.2%)	2	(0.1%)
Dry skin	1	(0.2%)	2	(0.1%)
Dermatitis contact	0		2	(0.1%)
Eczema	0		2	(0.1%)
Night sweats	0		2	(0.1%)
Dermatitis	1	(0.2%)	1	(<0.1%)
Granuloma annulare	0		1	(<0.1%)
Hyperkeratosis	0		1	(<0.1%)
Hypoaesthesia facial	0		1	(<0.1%)
Keratosis pilaris	0		1	(<0.1%)
Leukocytoclastic vasculitis	0		1	(<0.1%)
Onychoclasis	0		1	(<0.1%)
Periorbital oedema	0		1	(<0.1%)
Pruritus generalised	0		1	(<0.1%)
Psoriasis	0		1	(<0.1%)
Rash papular	0		1	(<0.1%)
Skin hyperpigmentation	0		1	(<0.1%)
Skin swelling	0		1	(<0.1%)
Dermatitis allergic	2	(0.4%)	0	
Skin lesion	2	(0.4%)	0	
Ecchymosis	1	(0.2%)	0	
Hair texture abnormal	1	(0.2%)	0	
Prurigo	1	(0.2%)	0	
Rash pruritic	1	(0.2%)	0	
Skin exfoliation	1	(0.2%)	0	
Vascular disorders	14	(3.0%)	43	(3.1%)
Hypertension	9	(1.9%)	26	(1.9%)
Orthostatic hypotension	1	(0.2%)	4	(0.3%)
Hypotension	1	(0.2%)	3	(0.2%)
Hypertensive crisis	0		3	(0.2%)
Hot flush	1	(0.2%)	2	(0.1%)
Venous insufficiency	1	(0.2%)	1	(<0.1%)
Aortic arteriosclerosis	0		1	(<0.1%)
Arterial thrombosis limb	0		1	(<0.1%)
Essential hypertension	0		1	(<0.1%)
Varicose vein	0		1	(<0.1%)
Vasculitis	0		1	(<0.1%)
Venous thrombosis	0		1	(<0.1%)
Haematoma	1	(0.2%)	0	
Investigations	14	(3.0%)	33	(2.4%)
Weight increased	4	(0.9%)	10	(0.7%)
Blood pressure increased	1	(0.2%)	3	(0.2%)
Transaminases increased	1	(0.2%)	3	(0.2%)
Blood creatinine increased	0		3	(0.2%)
Gamma-glutamyltransferase increased	2	(0.4%)	1	(<0.1%)

Alanine aminotransferase increased	1	(0.2%)	1	(<0.1%)
Aspartate aminotransferase increased	1	(0.2%)	1	(<0.1%)
Blood creatine phosphokinase increased	1	(0.2%)	1	(<0.1%)
Glycosylated haemoglobin increased	1	(0.2%)	1	(<0.1%)
Blood bilirubin increased	0		1	(<0.1%)
Blood glucose abnormal	0		1	(<0.1%)
Blood potassium increased	0		1	(<0.1%)
Blood triglycerides increased	0		1	(<0.1%)
Creatinine renal clearance decreased	0		1	(<0.1%)
Creatinine renal clearance increased	0		1	(<0.1%)
Electrocardiogram t wave abnormal	0		1	(<0.1%)
Electrocardiogram t wave inversion	0		1	(<0.1%)
Heart rate irregular	0		1	(<0.1%)
Hepatic enzyme increased	0		1	(<0.1%)
Liver function test abnormal	0		1	(<0.1%)
Blood cholesterol increased	1	(0.2%)	0	
Blood glucose increased	1	(0.2%)	0	
Blood testosterone decreased	1	(0.2%)	0	
Colonoscopy	1	(0.2%)	0	
Neutrophil count decreased	1	(0.2%)	0	
Occult blood positive	1	(0.2%)	0	
Weight decreased	1	(0.2%)	0	
Metabolism and nutrition disorders	10	(2.1%)	31	(2.3%)
Hypercholesterolaemia	3	(0.6%)	7	(0.5%)
Anorexia	0		3	(0.2%)
Diabetes mellitus	0		3	(0.2%)
Hyperglycaemia	3	(0.6%)	2	(0.1%)
Decreased appetite	1	(0.2%)	2	(0.1%)
Increased appetite	1	(0.2%)	2	(0.1%)
Dehydration	0		2	(0.1%)
Overweight	0		2	(0.1%)
Dyslipidaemia	0		1	(<0.1%)
Gout	0		1	(<0.1%)
Hyperkalaemia	0		1	(<0.1%)
Hyperlipidaemia	0		1	(<0.1%)
Hypoglycaemia	0		1	(<0.1%)
Iron deficiency	0		1	(<0.1%)
Lactose intolerance	0		1	(<0.1%)
Metabolic disorder	0		1	(<0.1%)
Type 2 diabetes mellitus	0		1	(<0.1%)
Fluid retention	1	(0.2%)	0	
Food craving	1	(0.2%)	0	
Hypokalaemia	1	(0.2%)	0	
Cardiac disorders	6	(1.3%)	31	(2.3%)
Palpitations	2	(0.4%)	10	(0.7%)
Tachycardia	1	(0.2%)	4	(0.3%)

Angina pectoris	0		2	(0.1%)
Arrhythmia	0		2	(0.1%)
Atrial fibrillation	0		2	(0.1%)
Coronary artery disease	0		2	(0.1%)
Cardiac failure	1	(0.2%)	1	(<0.1%)
Bundle branch block left	0		1	(<0.1%)
Cardiovascular disorder	0		1	(<0.1%)
Coronary artery occlusion	0		1	(<0.1%)
Left ventricular hypertrophy	0		1	(<0.1%)
Myocardial infarction	0		1	(<0.1%)
Myocardial ischaemia	0		1	(<0.1%)
Pericarditis	0		1	(<0.1%)
Supraventricular extrasystoles	0		1	(<0.1%)
Ventricular extrasystoles	0		1	(<0.1%)
Ventricular tachycardia	0		1	(<0.1%)
Arteriosclerosis coronary artery	1	(0.2%)	0	
Bradycardia	1	(0.2%)	0	
Cardiomyopathy	1	(0.2%)	0	
Reproductive system and breast disorders	11	(2.3%)	28	(2.0%)
Prostatitis	0		5	(0.4%)
Dysmenorrhoea	5	(1.1%)	4	(0.3%)
Benign prostatic hyperplasia	1	(0.2%)	2	(0.1%)
Testicular pain	0		2	(0.1%)
Vaginal discharge	0		2	(0.1%)
Amenorrhoea	1	(0.2%)	1	(<0.1%)
Erectile dysfunction	1	(0.2%)	1	(<0.1%)
Breast cyst	0		1	(<0.1%)
Breast disorder	0		1	(<0.1%)
Breast pain	0		1	(<0.1%)
Breast tenderness	0		1	(<0.1%)
Cervical polyp	0		1	(<0.1%)
Fibrocystic breast disease	0		1	(<0.1%)
Genital discharge	0		1	(<0.1%)
Genital haemorrhage	0		1	(<0.1%)
Genital pain	0		1	(<0.1%)
Haematospermia	0		1	(<0.1%)
Menopausal symptoms	0		1	(<0.1%)
Menstruation delayed	0		1	(<0.1%)
Metrorrhagia	0		1	(<0.1%)
Pelvic pain	0		1	(<0.1%)
Varicocele	0		1	(<0.1%)
Menstruation irregular	1	(0.2%)	0	
Ovarian torsion	1	(0.2%)	0	
Postmenopausal haemorrhage	1	(0.2%)	0	
Prostatomegaly	1	(0.2%)	0	
Uterine polyp	1	(0.2%)	0	

Eye disorders	10	(2.1%)	27	(2.0%)
Conjunctivitis	3	(0.6%)	4	(0.3%)
Dry eye	1	(0.2%)	4	(0.3%)
Vision blurred	0		4	(0.3%)
Retinal detachment	0		3	(0.2%)
Eye haemorrhage	0		2	(0.1%)
Eye irritation	0		2	(0.1%)
Eye pain	0		2	(0.1%)
Ocular hyperaemia	0		2	(0.1%)
Asthenopia	1	(0.2%)	1	(<0.1%)
Cataract	1	(0.2%)	1	(<0.1%)
Eyelid oedema	1	(0.2%)	1	(<0.1%)
Conjunctival haemorrhage	0		1	(<0.1%)
Conjunctivitis allergic	0		1	(<0.1%)
Eye inflammation	0		1	(<0.1%)
Glaucoma	0		1	(<0.1%)
Photophobia	0		1	(<0.1%)
Retinal tear	0		1	(<0.1%)
Visual acuity reduced	0		1	(<0.1%)
Blepharitis	1	(0.2%)	0	
Optic atrophy	1	(0.2%)	0	
Visual impairment	1	(0.2%)	0	
Ear and labyrinth disorders	0		20	(1.5%)
Tinnitus	0		10	(0.7%)
Vertigo	0		4	(0.3%)
Ear pain	0		2	(0.1%)
Cerumen impaction	0		1	(<0.1%)
Ear congestion	0		1	(<0.1%)
Motion sickness	0		1	(<0.1%)
Tympanic membrane disorder	0		1	(<0.1%)
Vertigo positional	0		1	(<0.1%)
Vestibular neuronitis	0		1	(<0.1%)
Immune system disorders	7	(1.5%)	12	(0.9%)
Seasonal allergy	3	(0.6%)	7	(0.5%)
Hypersensitivity	2	(0.4%)	3	(0.2%)
Drug hypersensitivity	0		2	(0.1%)
Food allergy	0		1	(<0.1%)
Allergy to arthropod bite	1	(0.2%)	0	
Allergy to arthropod sting	1	(0.2%)	0	
Renal and urinary disorders	6	(1.3%)	12	(0.9%)
Nephrolithiasis	2	(0.4%)	3	(0.2%)
Pollakiuria	2	(0.4%)	1	(<0.1%)
Stress urinary incontinence	1	(0.2%)	1	(<0.1%)
Dysuria	0		1	(<0.1%)
Haematuria	0		1	(<0.1%)

Hypertonic bladder	0		1	(<0.1%)
Nephropathy	0		1	(<0.1%)
Nocturia	0		1	(<0.1%)
Renal aneurysm	0		1	(<0.1%)
Renal colic	0		1	(<0.1%)
Calculus urethral	1	(0.2%)	0	
Micturition urgency	1	(0.2%)	0	
Urethral stenosis	1	(0.2%)	0	
Blood and lymphatic system disorders	2	(0.4%)	11	(0.8%)
Neutropenia	1	(0.2%)	4	(0.3%)
Anaemia	1	(0.2%)	3	(0.2%)
Lymphadenopathy	0		2	(0.1%)
Leukocytosis	0		1	(<0.1%)
Lymphadenitis	0		1	(<0.1%)
Lymphopenia	0		1	(<0.1%)
Leukopenia	1	(0.2%)	0	
Monocytopenia	1	(0.2%)	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.2%)	11	(0.8%)
Basal cell carcinoma	0		2	(0.1%)
Angiomyolipoma	0		1	(<0.1%)
Breast cancer	0		1	(<0.1%)
Gallbladder cancer metastatic	0		1	(<0.1%)
Lung adenocarcinoma	0		1	(<0.1%)
Neurofibroma	0		1	(<0.1%)
Seborrhoeic keratosis	0		1	(<0.1%)
Skin papilloma	0		1	(<0.1%)
Thyroid neoplasm	0		1	(<0.1%)
Uterine leiomyoma	0		1	(<0.1%)
Prostate cancer	1	(0.2%)	0	
Surgical and medical procedures	0		10	(0.7%)
Tooth extraction	0		2	(0.1%)
Bone graft	0		1	(<0.1%)
Carpal tunnel decompression	0		1	(<0.1%)
Cataract operation	0		1	(<0.1%)
Endometriosis ablation	0		1	(<0.1%)
Mammoplasty	0		1	(<0.1%)
Nail operation	0		1	(<0.1%)
Polypectomy	0		1	(<0.1%)
Skin neoplasm excision	0		1	(<0.1%)
Hepatobiliary disorders	3	(0.6%)	6	(0.4%)
Hepatic steatosis	1	(0.2%)	2	(0.1%)
Cholelithiasis	2	(0.4%)	1	(<0.1%)
Biliary colic	0		1	(<0.1%)
Biliary dyskinesia	0		1	(<0.1%)

Cholecystitis	0	1 (<0.1%)
Endocrine disorders	3 (0.6%)	3 (0.2%)
Autoimmune thyroiditis	0	1 (<0.1%)
Basedow's disease	0	1 (<0.1%)
Goitre	0	1 (<0.1%)
Hypothyroidism	2 (0.4%)	0
Toxic nodular goitre	1 (0.2%)	0
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	3 (0.2%)
Pregnancy	1 (0.2%)	3 (0.2%)
Social circumstances	0	2 (0.1%)
Family stress	0	1 (<0.1%)
Learning disability	0	1 (<0.1%)

Note: TEAE: Treatment emergent adverse event, SOC: System Organ Class, PT: Preferred Term.
Primary SOC and PT sorted by decreasing frequency in volinanserin 2mg/day then in placebo group.
Adverse events coded in MedDRA version 11.1

Deaths, serious adverse events, and treatment-emergent adverse events leading to study drug discontinuations

There was 1 death during the study. A 67-year-old female Caucasian in the volinanserin group developed adenocarcinoma of the gall bladder with liver and bone metastasis and died on Day 235 of the study. The adverse event was considered as unrelated to study treatment by the Investigator.

Serious adverse events are presented in the table below. Fifty-one patients, 11 (2.3%) in the placebo group and 40 (2.9%) in the volinanserin group, experienced serious TEAEs during the study. Injuries were the most common SAEs (serious adverse events) reported in the volinanserin group.

Number (%) of patients experiencing serious treatment-emergent adverse events presented by system organ class and preferred term – all-treated population

Primary System Organ Class	Placebo	Volinanserin 2mg/day
Any serious TEAE	11 (2.3%)	40 (2.9%)
Infections and infestations	1 (0.2%)	5 (0.4%)
Urinary tract infection	1 (0.2%)	1 (<0.1%)
Pneumonia	0	1 (<0.1%)
Helicobacter gastritis	0	1 (<0.1%)
Intervertebral discitis	0	1 (<0.1%)
Orchitis	0	1 (<0.1%)
Otitis media chronic	0	1 (<0.1%)
Nervous system disorders	2 (0.4%)	2 (0.1%)
Carotid artery stenosis	0	1 (<0.1%)
Subarachnoid haemorrhage	0	1 (<0.1%)
Cerebral infarction	1 (0.2%)	0
Petit mal epilepsy	1 (0.2%)	0
Gastrointestinal disorders	0	4 (0.3%)
Gastritis	0	1 (<0.1%)

Gastritis	0	1 (<0.1%)
Inguinal hernia	0	1 (<0.1%)
Duodenitis	0	1 (<0.1%)
Gastric ulcer haemorrhage	0	1 (<0.1%)
Musculoskeletal and connective tissue disorders	0	4 (0.3%)
Osteoarthritis	0	1 (<0.1%)
Intervertebral disc protrusion	0	2 (0.1%)
Loose body in joint	0	1 (<0.1%)
Injury, poisoning and procedural complications	1 (0.2%)	9 (0.7%)
Fall	0	1 (<0.1%)
Contusion	0	1 (<0.1%)
Road traffic accident	0	3 (0.2%)
Skin laceration	0	1 (<0.1%)
Meniscus lesion	0	1 (<0.1%)
Ankle fracture	0	2 (0.1%)
Soft tissue injury	0	1 (<0.1%)
Concussion	0	1 (<0.1%)
Rib fracture	0	1 (<0.1%)
Patella fracture	0	1 (<0.1%)
Pneumothorax traumatic	0	1 (<0.1%)
Post procedural complication	0	1 (<0.1%)
Renal injury	0	1 (<0.1%)
Splenic rupture	0	1 (<0.1%)
Traumatic fracture	0	1 (<0.1%)
Bursa injury	1 (0.2%)	0
Psychiatric disorders	1 (0.2%)	1 (<0.1%)
Confusional state	1 (0.2%)	0
Burnout syndrome	0	1 (<0.1%)
General disorders and administration site conditions	2 (0.4%)	1 (<0.1%)
Fatigue	1 (0.2%)	0
Chest pain	1 (0.2%)	0
Non-cardiac chest pain	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	0
Interstitial lung disease	1 (0.2%)	0
Vascular disorders	0	2 (0.1%)
Arterial thrombosis limb	0	1 (<0.1%)
Essential hypertension	0	1 (<0.1%)
Cardiac disorders	1 (0.2%)	4 (0.3%)
Angina pectoris	0	1 (<0.1%)
Coronary artery disease	0	1 (<0.1%)
Coronary artery occlusion	0	1 (<0.1%)

Myocardial infarction	0	1 (<0.1%)
Pericarditis	0	1 (<0.1%)
Ventricular tachycardia	0	1 (<0.1%)
Arteriosclerosis coronary artery	1 (0.2%)	0
Reproductive system and breast disorders	1 (0.2%)	1 (<0.1%)
Prostatitis	0	1 (<0.1%)
Ovarian torsion	1 (0.2%)	0
Eye disorders	0	1 (<0.1%)
Retinal detachment	0	1 (<0.1%)
Immune system disorders	0	1 (<0.1%)
Drug hypersensitivity	0	1 (<0.1%)
Renal and urinary disorders	0	1 (<0.1%)
Renal aneurysm	0	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2%)	4 (0.3%)
Basal cell carcinoma	0	1 (<0.1%)
Breast cancer	0	1 (<0.1%)
Gallbladder cancer metastatic	0	1 (<0.1%)
Lung adenocarcinoma	0	1 (<0.1%)
Prostate cancer	1 (0.2%)	0
Hepatobiliary disorders	0	1 (<0.1%)
Cholecystitis	0	1 (<0.1%)

Note: TEAE: Treatment emergent adverse event, SOC: System Organ Class, PT: Preferred Term.
Primary SOC and PT listed according to the order determined in the table of all TEAEs.
Adverse events coded in MedDRA version 11.1

TEAEs leading to treatment discontinuation

TEAEs that led to discontinuation of study drug are presented in the table below. Approximately 6% of patients in each treatment group discontinued study treatment due to a TEAE. Headache was the most common TEAE leading to treatment discontinuation in both treatment groups (0.6% of patients in the placebo group and 0.8% in the volinanserin group).

Summary of patients experiencing treatment-emergent adverse events leading to study drug discontinuation, presented by system organ class and preferred term – all-treated population

Primary system organ class	Placebo	Volinanserin 2mg/day
Any TEAE leading to study drug discontinuation	27 (5.7%)	90 (6.6%)
Infections and infestations	0	1 (<0.1%)
Lyme disease	0	1 (<0.1%)
Nervous system disorders	6 (1.3%)	33 (2.4%)
Headache	3 (0.6%)	11 (0.8%)
Somnolence	0	7 (0.5%)
Dizziness	2 (0.4%)	8 (0.6%)
Migraine	0	1 (<0.1%)

Migraine	0	1 (<0.1%)
Disturbance in attention	0	2 (0.1%)
Lethargy	0	3 (0.2%)
Tremor	0	1 (<0.1%)
Hypoaesthesia	0	1 (<0.1%)
Memory impairment	0	1 (<0.1%)
Sedation	0	1 (<0.1%)
Sinus headache	0	1 (<0.1%)
Cognitive disorder	0	1 (<0.1%)
Dysarthria	0	2 (0.1%)
Encephalopathy	0	1 (<0.1%)
Subarachnoid haemorrhage	0	1 (<0.1%)
Trigeminal neuralgia	0	1 (<0.1%)
Cerebral infarction	1 (0.2%)	0
Petit mal epilepsy	1 (0.2%)	0
Gastrointestinal disorders	5 (1.1%)	15 (1.1%)
Diarrhoea	0	2 (0.1%)
Nausea	0	4 (0.3%)
Constipation	0	1 (<0.1%)
Dry mouth	0	2 (0.1%)
Vomiting	1 (0.2%)	2 (0.1%)
Abdominal pain upper	1 (0.2%)	1 (<0.1%)
Gastritis	1 (0.2%)	0
Abdominal pain	0	1 (<0.1%)
Abdominal distension	1 (0.2%)	0
Gastric ulcer haemorrhage	0	1 (<0.1%)
Hypoaesthesia oral	0	1 (<0.1%)
Stomatitis	0	1 (<0.1%)
Lip dry	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	0	5 (0.4%)
Pain in extremity	0	1 (<0.1%)
Myalgia	0	1 (<0.1%)
Osteoarthritis	0	1 (<0.1%)
Musculoskeletal pain	0	1 (<0.1%)
Neck pain	0	1 (<0.1%)
Musculoskeletal chest pain	0	1 (<0.1%)
Injury, poisoning and procedural complications	2 (0.4%)	5 (0.4%)
Accidental overdose	1 (0.2%)	0
Fall	0	1 (<0.1%)
Contusion	0	1 (<0.1%)
Road traffic accident	0	1 (<0.1%)
Skin laceration	0	2 (0.1%)
Ankle fracture	0	1 (<0.1%)
Rib fracture	1 (0.2%)	1 (<0.1%)
Failure of implant	0	1 (<0.1%)

Pneumothorax traumatic	0	1 (<0.1%)
Renal injury	0	1 (<0.1%)
Splenic rupture	0	1 (<0.1%)
Traumatic fracture	0	1 (<0.1%)
Psychiatric disorders	8 (1.7%)	13 (0.9%)
Anxiety	2 (0.4%)	3 (0.2%)
Insomnia	1 (0.2%)	0
Depression	2 (0.4%)	5 (0.4%)
Abnormal dreams	1 (0.2%)	1 (<0.1%)
Depressed mood	1 (0.2%)	0
Initial insomnia	1 (0.2%)	0
Agitation	0	1 (<0.1%)
Nervousness	0	1 (<0.1%)
Confusional state	1 (0.2%)	0
Affect lability	0	1 (<0.1%)
Bipolar i disorder	0	1 (<0.1%)
Panic attack	0	1 (<0.1%)
Acute stress disorder	1 (0.2%)	0
General disorders and administration site conditions	3 (0.6%)	8 (0.6%)
Fatigue	2 (0.4%)	3 (0.2%)
Irritability	0	1 (<0.1%)
Pyrexia	1 (0.2%)	0
Malaise	0	2 (0.1%)
Facial pain	0	1 (<0.1%)
Feeling abnormal	0	1 (<0.1%)
Gait disturbance	0	1 (<0.1%)
Hangover	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	3 (0.6%)	2 (0.1%)
Dyspnoea	1 (0.2%)	0
Sleep apnoea syndrome	1 (0.2%)	2 (0.1%)
Interstitial lung disease	1 (0.2%)	0
Skin and subcutaneous tissue disorders	4 (0.9%)	2 (0.1%)
Rash	1 (0.2%)	0
Hyperhidrosis	1 (0.2%)	0
Acne	0	1 (<0.1%)
Alopecia	0	1 (<0.1%)
Dermatitis allergic	1 (0.2%)	0
Skin exfoliation	1 (0.2%)	0
Vascular disorders	0	5 (0.4%)
Hypertension	0	4 (0.3%)
Hot flush	0	1 (<0.1%)
Investigations	2 (0.4%)	2 (0.1%)

Blood creatinine increased	0	1 (<0.1%)
Gamma-glutamyltransferase increased	1 (0.2%)	0
Alanine aminotransferase increased	1 (0.2%)	1 (<0.1%)
Aspartate aminotransferase increased	1 (0.2%)	1 (<0.1%)
Neutrophil count decreased	1 (0.2%)	0
Metabolism and nutrition disorders	1 (0.2%)	0
Food craving	1 (0.2%)	0
Cardiac disorders	1 (0.2%)	9 (0.7%)
Tachycardia	1 (0.2%)	2 (0.1%)
Angina pectoris	0	2 (0.1%)
Arrhythmia	0	1 (<0.1%)
Atrial fibrillation	0	1 (<0.1%)
Coronary artery disease	0	1 (<0.1%)
Myocardial infarction	0	1 (<0.1%)
Pericarditis	0	1 (<0.1%)
Reproductive system and breast disorders	0	2 (0.1%)
Breast pain	0	1 (<0.1%)
Breast tenderness	0	1 (<0.1%)
Eye disorders	0	3 (0.2%)
Vision blurred	0	2 (0.1%)
Eye irritation	0	1 (<0.1%)
Immune system disorders	1 (0.2%)	0
Hypersensitivity	1 (0.2%)	0
Blood and lymphatic system disorders	0	1 (<0.1%)
Neutropenia	0	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (0.3%)
Basal cell carcinoma	0	1 (<0.1%)
Breast cancer	0	1 (<0.1%)
Gallbladder cancer metastatic	0	1 (<0.1%)
Lung adenocarcinoma	0	1 (<0.1%)
Endocrine disorders	0	2 (0.1%)
Basedow's disease	0	1 (<0.1%)
Goitre	0	1 (<0.1%)
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	3 (0.2%)
Pregnancy	1 (0.2%)	3 (0.2%)

Note: TEAE: Treatment emergent adverse event, SOC: System Organ Class, PT: Preferred Term.
Primary SOC and PT listed according to the order determined in the table of all TEAEs.
Adverse events coded in MedDRA version 11.1

Conclusions: [redacted]
Date of report: 13 July 2009