SYNOPSIS

Title of the study: A placebo controlled, randomized, 12-week, dose-ranging, double-blind study versus placebo using tolterodine as a study calibrator, to evaluate efficacy and safety of SSR240600C in women with overactive bladder including urge urinary incontinence (DRI6271/BILADY)
Investigators: No Coordinating Investigator was defined for the study
Study centers: There were 74 active centers located in North America (Canada, United States) and Europe (Czech Republic, France, Germany, Portugal)
Publications (reference): Not applicable
Study period: Date first patient enrolled: 15 November 2007 Date last patient completed: 07 February 2009
Phase of development: Phase 2B
Objectives: • **Primary objective:** To evaluate in females the effects of SSR240600C at 25, 50, or 100 mg on symptoms of overactive bladder as compared to placebo using tolterodine as a calibrator. • **Secondary objective**: To investigate the overall safety and tolerability of SSR240600C in the study population as compared to placebo and the study calibrator.
Methodology: This was a multicenter, randomized, double-blind, 5-arm, parallel-group study comparing 3 doses of SSR240600C (25, 50, and 100 mg) to placebo using tolterodine (Detrol® LA) as a calibrator. Patients were randomized to 1 of 5 treatment groups in a 1:1:1:1:1 fashion.
Number of patients: Planned: 800 (160 per group) Randomized: 345 (The enrollment was stopped in September 2008 and the enrolled patients were allowed to continue till the completion of the study) Treated: 334 Evaluated: Efficacy: 332 Safety : 334 Pharmacokinetics : Not applicable
Diagnosis and criteria for inclusion: Females ≥18 and ≤75 years of age with diagnosis of overactive bladder with symptoms of urgency with urge incontinence and frequency (≥1 urgency episode per day, ≥8 micturitions per day, ≥5 urge urinary incontinence [UUI] episodes/week), which could be associated with nocturia, but without bladder pain.
Investigational product: SSR240600C (25 or 50 mg in size 0 capsules) Doses: 25, 50, or 100 mg once daily in the morning Administration: oral with food Batch numbers: [redacted] CL-11693, CL-11834, CL-12314, CL-12694, CL-13215, CL-12941
Reference therapy: Placebo (matching capsules) Dose: Not applicable Administration: oral with food Batch number(s): [redacted]

Calibrator: Tolterodine 4 mg tablets (Detrol® LA) encapsulated in size 0 capsules

Dose: 4 mg once daily

Administration: oral with food

Batch number(s): [redacted]

Duration of treatment: 12 weeks

Duration of observation: approximately 18 weeks including a 1 to 3 week screening period, a 12-week double-blind treatment period, and a 4-week follow-up period.

Criteria for evaluation:

Demographic and baseline characteristics

Demographic and baseline characteristics included race, age, age group (18 to 44, 45 to 64, ≥65 years), weight, height, and body mass index (BMI); patient index of anxiety and depression based on Hamilton scale at Visit 2, previous medication used for the treatment of overactive bladder, and concomitant medications.

Efficacy:

Primary efficacy variable: Mean change from baseline to Week 12 in the number of micturitions per 24 hours.

Key secondary efficacy variables:

- Mean change from baseline to Week 12 in the number of urgency episodes per 24 hours
- Mean change from baseline to Week 12 in the number of UUI episodes per 24 hours

Safety:

The safety variables included adverse events that were reported spontaneously or observed by the Investigator, laboratory parameters, vital signs, body weight, and electrocardiograms (ECGs).

Statistical methods:

Because this study was terminated after randomization of 345 of the 800 patients, only limited efficacy assessments and descriptive tabulations are presented. No pharmacokinetic analyses were performed.

Efficacy:

- **Primary efficacy analysis:** The analysis of the primary efficacy variable was performed using the modified intent-to-treat (mITT) population, which was defined as all randomized patients who took at least 1 dose of the investigational product and had baseline and at least 1 postbaseline efficacy assessment. This analysis was performed using an analysis of covariance (ANCOVA) model, which included treatment and pooled center as fixed effects and baseline as a covariate. The statistical tests comparing each of the SSR240600C doses and tolterodine with placebo, as well as 95% confidence intervals for all pairwise differences were derived from this model. The testing of the 3 SSR240600C doses against placebo was adjusted using the Hochberg procedure, and the testing of tolterodine over placebo was not adjusted for multiplicity as the test was to provide evidence as to whether the trial was well conducted. The last-observation-carried-forward approach was carried out to impute the missing Week 12 evaluation on number of micturitions per 24 hours.
- **Secondary efficacy analyses:** The 2 secondary efficacy variables (number of urgency episodes per 24 hours and number of UUI episodes per 24 hours) were analyzed in the same way as for the primary efficacy variable.

Safety:

Safety population was all patients exposed to study medication regardless of the amount of medication administered.

Evaluation of the safety data was based on the review of individual values and descriptive statistics. The focus of adverse event reporting was on treatment-emergent adverse events. The number and percentage of patients with treatment-emergent adverse events, classified by MedDRA system organ class and preferred term were tabulated by treatment group. All adverse events were listed by patients. Potentially clinically significant abnormalities in clinical laboratory test results, vital signs, and ECG parameters were flagged and summarized for each treatment group.

Summary:

The Sponsor decided to stop the DRI6271 study before reaching its full enrollment. This was a company decision which was not related to any safety issue or any clinical problem. This study was terminated prior to enrolling the planned 800 patients. Therefore, the efficacy assessments were limited to the primary efficacy variable and the 2 key secondary efficacy variables. No pharmacokinetic analyses were performed.

The original sample size calculations (800 patients in total, or 160 patients per group) were performed based on the primary endpoint of the study. The study was stopped early with 345 randomized patients (approximately 70 patients per group). With 70 patients per group, the study had 80% power to detect a difference larger than originally assumed between SSR240600C and placebo, ie, a difference of -1.7 in number of micturitions per 24 hours using a 2-sided $\alpha = 0.0167$ and an SD of 3.1. The selection of $\alpha = 0.0167$ was carried out by applying the Hochberg procedure to adjust multiplicity. SD = 3.1 used in power calculation, was chosen from similar trials for tolterodine and from the in-house study MILADY (ACT5190).

Disposition of subjects:

Of the 345 patients randomized and 334 patients treated with investigational product, 51 patients discontinued the study treatments. Adverse events, lack of efficacy, and "Other reason" were the main reasons for study discontinuations. A by-subject listing of reasons included in "Other reason" category is presented in the CSR.

Summary of disposition of patients - Randomized patients

	Placebo (N=71)	SSR240600C 25mg (N=72)	SSR240600C 50mg (N=66)	SSR240600C 100mg (N=70)	Tolterodine 4mg (N=66)
Randomized and treated					
Completed treatment period	56 (78.9%)	63 (87.5%)	55 (83.3%)	53 (75.7%)	56 (84.8%)
Treatment discontinuations	10 (14.1%)	8 (11.1%)	9 (13.6%)	15 (21.4%)	9 (13.6%)
Reason for treatment discontinuation:					
Adverse event	2 (2.8%)	3 (4.2%)	4 (6.1%)	6 (8.6%)	4 (6.1%)
Lack of efficacy	3 (4.2%)	1 (1.4%)	2 (3.0%)	2 (2.9%)	0
Poor compliance to protocol	2 (2.8%)	1 (1.4%)	0	2 (2.9%)	1 (1.5%)
Lost to follow-up	0	0	1 (1.5%)	1 (1.4%)	0
Other reason	3 (4.2%)	3 (4.2%)	2 (3.0%)	4 (5.7%)	4 (6.1%)
Treatment discontinuation:					
Subject's decision	8 (11.3%)	7 (9.7%)	6 (9.1%)	9 (12.9%)	7 (10.6%)
Not a subject's decision	2 (2.8%)	1 (1.4%)	3 (4.5%)	6 (8.6%)	2 (3.0%)

% calculated using the number of randomized patients (N) as denominator.

Demographic and baseline characteristics:

The majority of the patients randomized in this study was Caucasian. The demographic and baseline characteristics of the patients were similar across the treatment groups. Demographic characteristics of the patients are summarized below.

Summary of demographic and baseline patient characteristics - mITT population

	Placebo (N=65)	SSR240600C 25mg (N=71)	SSR240600C 50mg (N=63)	SSR240600C 100mg (N=68)	Tolterodine 4mg (N=65)
Age (years)					
Number	65	71	63	68	65
Mean (SD)	55.0 (10.2)	55.2 (10.2)	52.7 (11.9)	52.5 (10.9)	53.5 (12.3)
Median	57.0	56.0	55.0	54.0	56.0
Min : Max	23 : 70	28 : 70	22 : 70	23 : 70	21 : 73
Age group					
18 - 44 years	8 (12.3%)	12 (16.9%)	15 (23.8%)	13 (19.1%)	14 (21.5%)
45 - 64 years	46 (70.8%)	42 (59.2%)	36 (57.1%)	46 (67.6%)	38 (58.5%)
≥ 65 years	11 (16.9%)	17 (23.9%)	12 (19.0%)	9 (13.2%)	13 (20.0%)
Race					
American Indian	0	1 (1.4%)	0	0	0
Asian/Oriental	0	0	0	1 (1.5%)	1 (1.5%)
Black	2 (3.1%)	8 (11.3%)	8 (12.7%)	11 (16.2%)	6 (9.2%)
Caucasian/White	63 (96.9%)	62 (87.3%)	55 (87.3%)	55 (80.9%)	58 (89.2%)
Native Hawaiian	0	0	0	1 (1.5%)	0
Ethnicity					
Hispanic	6 (9.2%)	5 (7.0%)	5 (7.9%)	5 (7.4%)	5 (7.7%)
Not Hispanic	57 (87.7%)	57 (80.3%)	50 (79.4%)	51 (75.0%)	53 (81.5%)
Missing	2 (3.1%)	9 (12.7%)	8 (12.7%)	12 (17.6%)	7 (10.8%)
Sex					
Female	65 (100%)	71 (100%)	63 (100%)	68 (100%)	65 (100%)
Weight (kg)					
Number	65	71	63	68	65
Mean (SD)	81.21 (21.04)	84.70 (24.82)	82.01 (21.39)	75.44 (17.26)	77.45 (18.48)
Median	78.00	75.90	78.60	74.50	77.10
Min : Max	51.4 : 136.1	54.5 : 175.5	46.0 : 136.4	46.0 : 129.5	50.0 : 126.0
Height (cm)					
Number	65	71	63	68	65
Mean (SD)	162.25 (7.77)	162.76 (6.73)	162.98 (8.08)	162.38 (8.02)	161.87 (7.39)
Median	161.00	161.00	162.56	162.00	161.29
Min : Max	144.0 : 180.3	152.0 : 180.3	150.5 : 187.9	140.0 : 183.0	140.0 : 177.8
BMI (kg/m^2)[a]					
Number	65	71	63	68	65
Mean (SD)	30.84 (7.70)	31.89 (8.61)	30.80 (7.52)	28.70 (6.76)	29.55 (6.82)
Median	30.19	29.76	29.67	27.85	29.23
Min : Max	16.1 : 54.0	19.4 : 64.4	19.1 : 54.2	17.7 : 51.9	18.6 : 54.1

[a]Body mass index (BMI) = weight (kg)/(height (m) * height (m)).

Efficacy results:

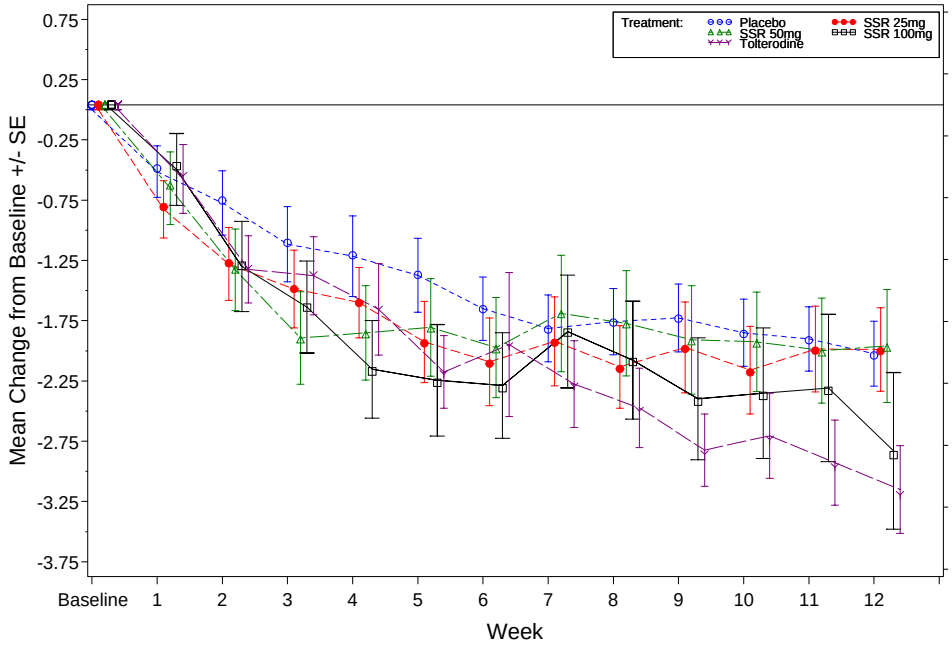
- Primary efficacy variable: No statistically significant difference was observed with any of the SSR240600C dose groups (25, 50, and 100 mg) compared with the placebo group. The highest SSR240600C dose group (100 mg) demonstrated a numerical improvement over placebo. The tolterodine group showed statistically significant improvement over placebo without any multiplicity adjustment, which provided evidence for the validity of the trial.

Mean change from baseline to Week 12 (last observation carried forward) in the number of micturitions per 24 hours – mITT population

Number of micturitions per 24 hours	Placebo (N=65)	SSR240600C 25mg (N=71)	SSR240600C 50mg (N=63)	SSR240600C 100mg (N=68)	Tolterodine 4mg (N=65)
Baseline					
Number	65	70	63	65	63
Mean (SD)	10.42 (1.98)	10.88 (2.94)	10.69 (3.19)	10.68 (3.00)	10.99 (2.46)
Median	10.29	10.43	10.14	9.86	10.43
Week 12					
Number	65	70	63	65	63
Mean (SD)	8.40 (2.74)	8.52 (2.76)	8.57 (2.76)	7.93 (2.98)	7.77 (2.67)
Median	7.71	8.57	8.00	7.33	7.57
Change from baseline					
Number	65	70	63	65	63
Mean (SD)	-2.02 (2.45)	-2.36 (2.88)	-2.13 (3.31)	-2.75 (4.02)	-3.22 (2.61)
Median	-2.29	-2.08	-2.48	-3.10	-3.11
LS mean (SE)[a]	-2.15 (0.33)	-2.22 (0.32)	-2.10 (0.34)	-2.71 (0.33)	-3.09 (0.34)
95% CI	(-2.80 to -1.50)	(-2.85 to -1.59)	(-2.78 to -1.43)	(-3.37 to -2.06)	(-3.76 to -2.41)
LS mean difference vs. Placebo					
Estimate (SE)[a]	-	-0.08 (0.45)	0.05 (0.47)	-0.56 (0.46)	-0.94 (0.47)
95% CI	-	(-0.97 to 0.82)	(-0.87 to 0.97)	(-1.47 to 0.34)	(-1.87 to -0.01)
P-value	-	0.8689	0.9189	0.2233	0.0467
Adjusted p-value[b]	-	0.9189	0.9189	0.6699	-
LS mean difference vs. Tolterodine					
Estimate (SE)[a]	-0.94 (0.47)	-0.86 (0.46)	-0.99 (0.47)	-0.38 (0.47)	-
95% CI	(-1.87 to -0.01)	(-1.77 to 0.04)	(-1.92 to -0.06)	(-1.30 to 0.54)	-

SD = standard derivation, CI = confidence interval, SE = standard error.
[a] ANCOVA model adjusted for baseline and pooled centers.
[b] P-Values were adjusted using the Hochberg procedure.

Mean change from baseline for number of micturitions per 24 hours at each week – mITT population



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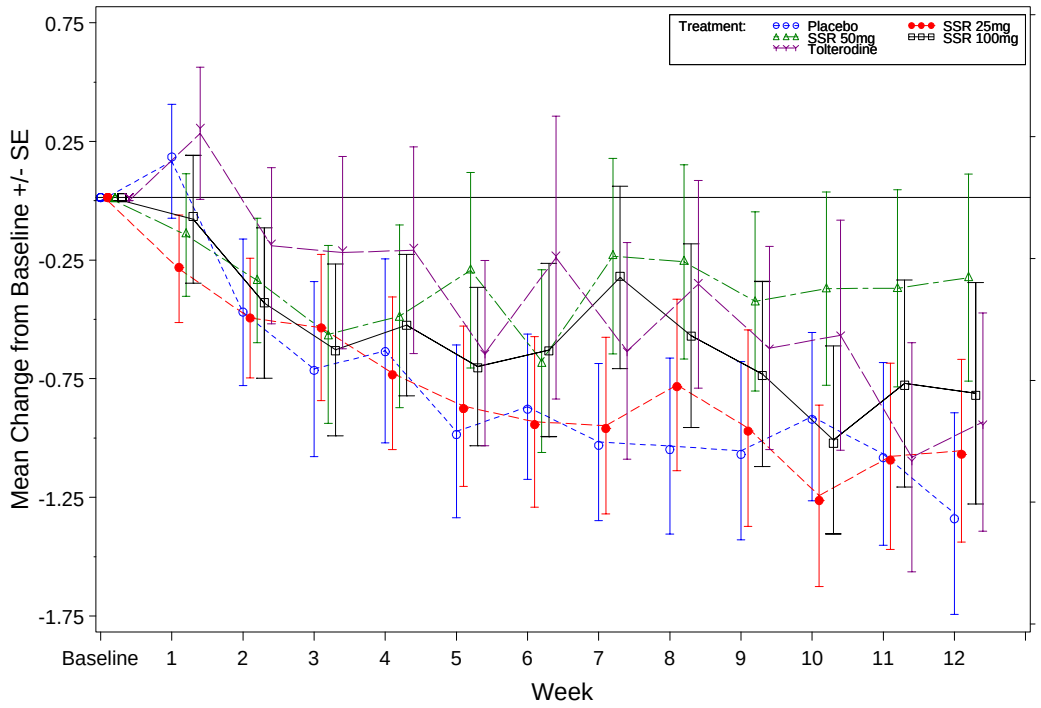
- Secondary efficacy variables: No statistically significant differences were observed for any of the SSR240600C dose groups compared with the placebo group in the mean changes from baseline to Week 12 in the number of UUI episodes per 24 hours, number of urgency episodes per 24 hours. The tolterodine group showed numerical improvement over placebo for the UUI episodes variable; however, it did not reach the statistical significance at the 5% level.

Mean change from baseline to Week 12 (last observation carried forward) in the number of urgency episodes per 24 hours - mITT population

Number of urgency episodes per 24 hours	Placebo (N=65)	SSR240600C 25mg (N=71)	SSR240600C 50mg (N=63)	SSR240600C 100mg (N=68)	Tolterodine 4mg (N=65)
Baseline					
Number	65	70	62	64	63
Mean (SD)	6.98 (3.47)	6.62 (3.82)	6.84 (3.75)	6.44 (3.51)	6.75 (3.12)
Median	6.67	6.00	6.57	6.71	6.83
Week 12					
Number	65	70	62	64	63
Mean (SD)	5.64 (3.58)	5.52 (3.48)	6.27 (3.71)	5.07 (3.22)	5.53 (2.77)
Median	5.33	5.08	5.83	5.42	5.67
Change from baseline					
Number	65	70	62	64	63
Mean (SD)	-1.33 (3.16)	-1.10 (2.83)	-0.57 (2.93)	-1.37 (3.08)	-1.22 (3.15)
Median	-0.93	-0.91	-1.00	-1.15	-1.71
LS mean (SE)[a]	-1.25 (0.34)	-1.17 (0.33)	-0.55 (0.35)	-1.52 (0.34)	-1.34 (0.35)
95% CI	(-1.92 to -0.59)	(-1.81 to -0.53)	(-1.25 to 0.14)	(-2.19 to -0.84)	(-2.03 to -0.65)
LS mean difference vs. Placebo					
Estimate (SE)[a]	-	0.08 (0.46)	0.70 (0.48)	-0.27 (0.47)	-0.09 (0.48)
95% CI	-	(-0.83 to 0.99)	(-0.24 to 1.64)	(-1.19 to 0.66)	(-1.03 to 0.85)
P-value	-	0.8626	0.1460	0.5737	0.8557
LS mean difference vs. Tolterodine					
Estimate (SE)[a]	-0.09 (0.48)	-0.17 (0.47)	-0.78 (0.48)	0.18 (0.48)	-
95% CI	(-1.03 to 0.85)	(-1.09 to 0.76)	(-1.73 to 0.17)	(-0.76 to 1.12)	-

SD = standard derivation, CI = confidence interval, SE = standard error.
[a] ANCOVA model adjusted for baseline and pooled centers.

Change from baseline for number of urgency episodes per 24 hours at each week – mITT population



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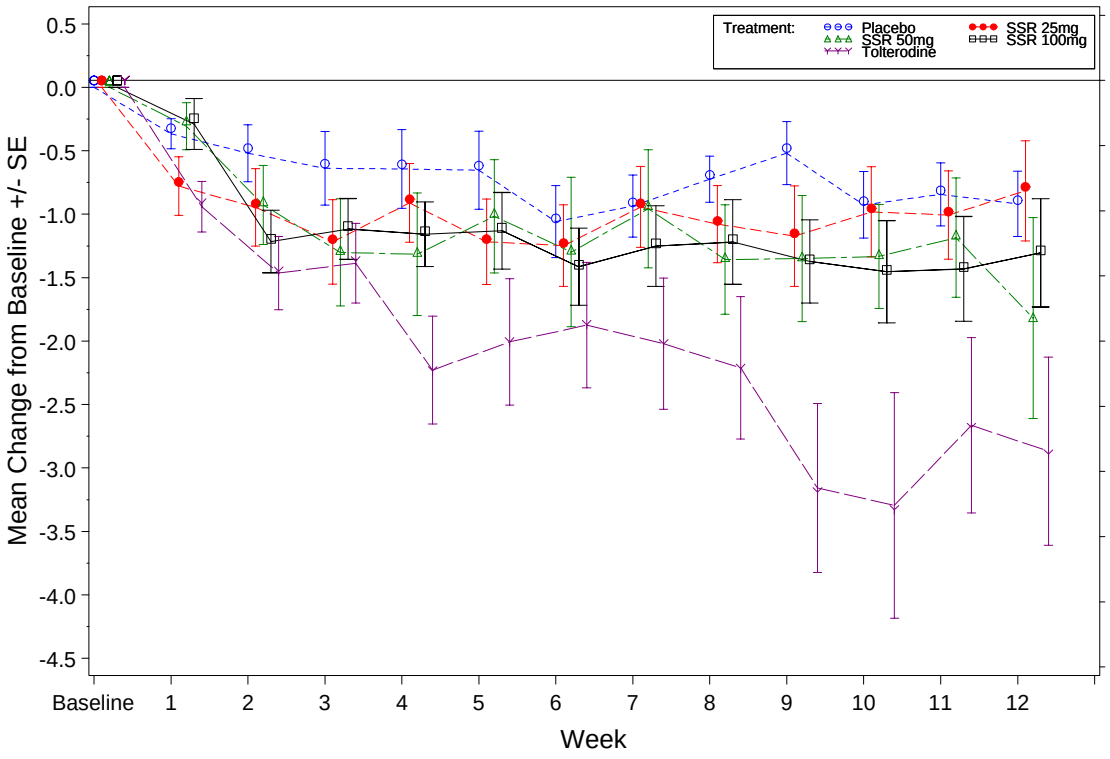
Mean change from baseline to Week 12 (last observation carried forward) in the number of urgent urinary incontinence per 24 hours - mITT population

Number of UUI per 24 hours	Placebo (N=65)	SSR240600C 25mg (N=71)	SSR240600C 50mg (N=63)	SSR240600C 100mg (N=68)	Tolterodine 4mg (N=65)
Baseline					
Number	63	65	61	57	54
Mean (SD)	2.90 (1.77)	3.91 (2.67)	3.11 (2.76)	3.11 (1.97)	3.76 (3.38)
Median	2.20	3.17	2.00	2.40	2.38
Week 12					
Number	63	65	61	57	54
Mean (SD)	1.79 (1.08)	2.37 (2.72)	1.81 (1.26)	1.89 (1.53)	1.75 (1.61)
Median	1.33	1.33	1.33	1.33	1.33
Change from baseline					
Number	63	65	61	57	54
Mean (SD)	-1.12 (1.42)	-1.54 (2.36)	-1.30 (2.73)	-1.22 (1.76)	-2.02 (2.29)
Median	-0.80	-1.14	-0.67	-1.00	-1.15
LS mean (SE)[a]	-1.28 (0.18)	-1.14 (0.18)	-1.37 (0.19)	-1.25 (0.19)	-1.68 (0.20)
95% CI	(-1.64 to -0.93)	(-1.50 to -0.78)	(-1.74 to -1.00)	(-1.63 to -0.88)	(-2.07 to -1.28)
LS mean difference vs. Placebo					
Estimate (SE)[a]	-	0.15 (0.25)	-0.09 (0.26)	0.03 (0.26)	-0.39 (0.27)
95% CI	-	(-0.36 to 0.65)	(-0.59 to 0.42)	(-0.48 to 0.54)	(-0.92 to 0.14)
P-value	-	0.5691	0.7347	0.9078	0.1454
LS mean difference vs. Tolterodine					
Estimate (SE)[a]	-0.39 (0.27)	-0.54 (0.26)	-0.30 (0.27)	-0.42 (0.27)	-
95% CI	(-0.92 to 0.14)	(-1.06 to -0.02)	(-0.83 to 0.22)	(-0.96 to 0.12)	-

SD = standard derivation, CI = confidence interval, SE = standard error.
[a] ANCOVA model adjusted for baseline and pooled centers.

Change from baseline for number of urgent urinary incontinence episodes per 24 hours at each week – mITT population



Safety results:

Of the 345 randomized patients, 332 patients were exposed to the investigational product.

Extent of exposure - mITT population

	Placebo (N=65)	SSR240600C 25mg (N=71)	SSR240600C 50mg (N=63)	SSR240600C 100mg (N=68)	Tolterodine 4mg (N=65)
Extent of exposure (Days)					
Number	65	71	63	68	65
Mean (SD)	128.7 (86.6)	129.8 (84.0)	115.0 (70.5)	126.4 (88.9)	123.5 (71.3)
Median	85.0	85.0	84.0	84.0	85.0
Min : Max	14 : 387	18 : 469	11 : 367	1 : 393	7 : 322
Number (%) of patients					
1 - 7 days	0	0	0	4 (5.9%)	1 (1.5%)
8 - 14 days	1 (1.5%)	0	1 (1.6%)	1 (1.5%)	0
15 - 29 days	3 (4.6%)	2 (2.8%)	2 (3.2%)	0	2 (3.1%)
30 - 84 days	26 (40.0%)	33 (46.5%)	29 (46.0%)	31 (45.6%)	27 (41.5%)
>84 days	35 (53.8%)	36 (50.7%)	31 (49.2%)	32 (47.1%)	35 (53.8%)

% calculated using the number of safety patients as the denominator.

Overview of treatment-emergent adverse events - Safety population

	Placebo (N=66)	SSR240600C 25mg (N=71)	SSR240600C 50mg (N=64)	SSR240600C 100mg (N=68)	Tolterodine 4mg (N=65)
Patients with any TEAE	34 (51.5%)	31 (43.7%)	36 (56.3%)	38 (55.9%)	36 (55.4%)
Patients with any serious TEAE	0	1 (1.4%)	1 (1.6%)	0	0
Patients discontinued treatment due to a TEAE	2 (3.0%)	3 (4.2%)	3 (4.7%)	6 (8.8%)	4 (6.2%)
Patients with any TEAE leading to death	0	0	0	0	0

TEAE = treatment-emergent adverse event.
% calculated using the number of safety patients in each group as the denominator.
MedDRA version: 11.0.

The overall incidence of treatment-emergent adverse events (TEAEs) was similar among the treatment groups. The most prevalent TEAEs in all treatment groups were gastrointestinal disorders with mainly diarrhea, dry mouth, dyspepsia, and constipation, and infections with mainly cystitis and nasopharyngitis (a summary table of TEAEs is presented in the CSR.

No deaths were reported.

Two serious TEAEs of ventricular tachycardia and postprocedural hemorrhage were reported.

A 63 year old female patient (Patient number [redacted]) with a history of chronic stable angina experienced palpitations, not associated with chest pain, about 2 months after the first administration of SSR240600C 25 mg. Her cardiac home monitoring recorded 9 beats of nonsustained ventricular tachycardia and her blood pressure was 200/90 mmHg. The study treatment was permanently discontinued. During hospitalization, myocardial infarcation was ruled out and the electrocardiogram was unremarkable with normal QTc interval. Electrophysiology monitoring showed no inducible ventricular arrhythmias.

A 30 years old female patient (Patient number [redacted]) admitted with suspected pelvic neoplasm and underwent laparoscopic surgery, experienced postprocedural hemorrhage, about 2 months after the first administration of SSR240600C 50 mg. Blood test showed a drop of hemoglobin up to 3.7 g/dl. Computed tomography scan showed a large amount of fluid in her pelvis and abdomen. Two units of fresh frozen plasma transfusion were given. Exploratory laparoscopy was performed with hemostasis of the operative sites. The surgical pathology tests showed benign cystic teratoma (dermoid cyst). She permanently discontinued the study treatment 1 week before her admission due to this prescheduled surgery.

Neither of the 2 serious TEAE events were considered to be related to the study drug by both the Investigator and the Sponsor. Both patients recovered without sequelae.

A total of 18 patients withdrew from the study treatment due to adverse events of gastrointestinal disorders and nervous system disorders. The rates of discontinued events were similar across the treatment groups except in the SSR240600C 100 mg group where a numerically higher rate was observed (a summary table of TEAEs leading to discontinuations is presented in thte CSR.

With respect to hepatic enzyme elevations, 3 patients (1 each in placebo, 25 mg SSR240600C, and 4 mg tolterodine group) were found to have >1.5 x upper limit of normal (ULN) of alkaline phosphatase, 2 patients (1 each in placebo and 4 mg tolterodine group) had isolated >3 x ULN of ALT, 2 patients (1 each in 25 mg and 100 mg SSR240600C group) reported >1.5 x ULN total bilirubin, and 2 patients (1 each in 25 mg SSR240600C and 100 mg SSR240600C group) reported >2 x ULN total bilirubin. There were no patients with associated ALT >3 x ULN and total bilirubin >2 x ULN.

Vital signs and electrocardiogram parameters were mostly similar across the treatment groups and did not present any special concerns.

Conclusions

[redacted]

Date of report: 08-Jul-2009