

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-103

MEDICAL REVIEW(S)

Medical Team Leader's Memorandum
Food and Drug Administration
ODE 3
Division of Reproductive and Urologic Products (DRUP)

Date: July 27, 2007

From: Suresh Kaul, MD, MPH, Acting Medical Team Leader, DRUP

To: Mark S. Hirsch, M.D., Acting Deputy Director, DRUP

Subject: NDA 22,103
Sanctura XR (trospium chloride) 60mg Tablet for the treatment of overactive bladder with symptoms of urinary frequency, urgency and urge urinary incontinence.

1. Executive summary and recommendation

The purpose of this memo is to provide the Deputy Division Director with my recommendation regarding regulatory action on this NDA. At this time, **I recommend that Sanctura XR should be approved for the treatment of overactive bladder (OAB) with symptoms of urinary frequency and urge urinary incontinence.** This NDA contains substantial evidence that Sanctura XR is effective and safe as labeled for the treatment of overactive bladder (OAB). The sponsor has demonstrated through two randomized, placebo-controlled trials that the benefits of Sanctura XR are apparent as early as one week and that the adverse events such as dry mouth and constipation commonly occurred within the first two weeks of treatment. There are no outstanding issues.

2. Clinical background

Overactive bladder (OAB) is a common disorder affecting millions of Americans. It is prevalent among middle-aged females and females greater than 75 years of age, but it also exists in men. OAB symptoms include urinary frequency and urge urinary incontinence. OAB is related to the presence of involuntary contractions of the detrusor (bladder wall) smooth muscle that results in a decrease in the ability to store urine. In some patients, involuntary detrusor contractions are directly related to a known neurological condition and in these patients, the condition is referred to as detrusor hyperreflexia.

In OAB, therapy is generally directed at the bladder wall smooth muscle, with the objective of relaxing the bladder so that it is capable of holding more urine for a longer period of time prior to experiencing an involuntary contraction. Therapy is intended to relieve the following symptoms: a need to urinate immediately (urgency), increased urinary frequency (voids) and incontinence.

The mainstay of treatment for OAB has been and continues to be anticholinergic medications. These include tolterodine (Detrol and Detrol LA) and oxybutynin (Ditropan, Ditropan XL, and Oxytrol), trospium chloride (Sanctura), solifenacin (Vesicare) and darifenacin (Enablex). Treatment of OAB with anticholinergics has been limited by well-recognized side effects including dry mouth, constipation, urinary retention, tachycardia, and changes in mental status.

In this NDA, the sponsor has proposed trospium chloride 60mg once daily for the treatment of OAB. Trospium chloride is a fairly old compound that is approved in Europe for treatment of urinary incontinence for at least a decade. Trospium chloride was approved as Sanctura 20mg BID in the United States for the treatment of OAB in 2004. The sponsor has developed a 60 mg once-daily formulation that they believe is effective in relieving OAB symptoms with an acceptable tolerability profile. The potential benefits of this medication over currently available treatments include the fact that a large part of Sanctura XR is eliminated through ester hydrolysis and active renal secretion, not through hepatic cytochrome P450 metabolism. This property limits the potential for pharmacokinetic drug interactions. Further, Sanctura XR is a charged molecule and is believed to have less penetration into the central nervous system resulting in fewer CNS-related side effects, such as delirium and sedation. Finally, the once-daily dosing regimen offers convenience and a potential compliance benefit over the twice daily IR regimen.

Reviewer's comments:

- 1. Despite the belief that Sanctura XR causes reduced CNS-related adverse reactions, there is not enough compelling evidence to conclude that Sanctura XR is better than other anticholinergic medications for CNS-related adverse reactions.**
- 2. Nevertheless, this clinical reviewer believes that Sanctura XR offers another option in OAB treatment with less prominent adverse events such as dry mouth and constipation in a once-daily formulation.**

In support of this NDA 22-103, the sponsor submitted data from 2 pivotal Phase-3 trials (IP631-018 and IP631-022) involving 1165 subjects at 117 U.S. study sites. In addition, this NDA submission includes data from 3 Phase-1 pharmacokinetic studies (82 subjects) and a single Phase-2 study (148 subjects). This medical team leader's memorandum focuses on the U.S., Phase 3 trial results.

The design of the 2 pivotal studies was similar. The only meaningful difference in the studies was the inclusion of a population PK substudy in study -018. This allowed for an integration of the clinical database for analyses. Both studies were double-blind, randomized, placebo-controlled and conducted for 12 weeks with an optional 9-month open-label extension. Study - 018 enrolled 601 subjects at 55 sites, and Study - 022 enrolled 564 subjects at 62 sites. The eligibility criteria and the criteria for evaluation of efficacy and safety were the similar for both studies.

The study objectives were to evaluate the effects of once daily dosing of Sanctura XR compared to placebo on urinary frequency, urge urinary incontinence, and other related symptoms associated with OAB over a 12 week treatment period.

3. Design of the controlled studies submitted in support of the application

In support of the efficacy and safety of Sanctura XR for the OAB indication, the sponsor submitted the results from:

- IP631-018 - a pivotal study, Phase-3**
- IP631-022 - a pivotal study, Phase-3**
- IP631-011 - a supporting study, Phase-1**
- IP631-019 - a supporting study, Phase-1**
- IP631-020 - a supporting study, Phase-1**
- IP631-016 - a supporting study, Phase-2**

The design of the two phase 3 studies was similar and is described briefly herein:
 The 2 pivotal trials were randomized, multi-center, double-blind, placebo-controlled, parallel group studies of efficacy and safety conducted in the US for a term of 12 weeks. There was an optional 9 month open label extension.

Both studies collected urinary data, derived from urinary diaries, on toilet void frequency, the urgency severity associated with each toilet void, and the number of incontinence episodes for 3 days prior to the baseline, and at weeks 1, 4, and 12 visits. Data for volume voided was collected for 2 days prior to these visits.

Reviewers comment: The eligibility criteria, study designs, and urinary diary data collection procedures were reasonable for the pivotal studies.

4. Clinical results to support the indication

4.1 Efficacy

The efficacy results from both Phase 3, efficacy and safety studies (Studies – 018 and – 022) revealed that Sanctura XR was associated with clinically relevant and statistically significant reductions in urinary frequency, urge incontinence episodes, and volume void compared to placebo. Table 1 and Figures 2 and 3 present the critical efficacy information for Study –018. The co-primary endpoints in the trials were the mean change from baseline to Week 12 in number of voids/24 hours (reductions in urinary frequency) and the mean change from baseline to Week 12 in number of incontinence episodes/24 hours. Key secondary endpoints included mean change from baseline to Week 12 in volume per void.

Study 1 included 592 patients in both SANCTURA XR 60 mg and placebo groups.

SANCTURA XR demonstrated statistically significantly ($p < .01$) greater reductions in the urinary frequency and incontinence episodes, and increases in void volume when compared to placebo starting at Week 1 and maintained through Weeks 4 and 12.

Table 1: Summarized Efficacy Results for Study -018
Mean Change from Baseline in Urinary Frequency, Urge Incontinence Episodes and Volume Void

Efficacy Endpoint	Week	Placebo	SANCTURA XR	P-Value
Urinary frequency / 24 hours		(N = 300)	(N = 292)	
Mean Baseline	0	12.7 (0.2)	12.8 (0.2)	
Mean Change from Baseline	1	-1.2 (0.1)	-1.7 (0.1)	0.0092
	4	-1.6 (0.2)	-2.4 (0.2)	<0.0001
	12	-2.0 (0.2)	-2.8 (0.2)	<0.0001
Urge incontinence episodes / week		(N = 300)	(N = 292)	
Mean Baseline	0	29.0 (1.3)	28.8 (1.3)	
Mean Change from Baseline	1	-8.7 (1.0)	-13.0 (0.9)	0.0003
	4	-12.2 (1.1)	-16.5 (1.2)	0.0054
	12	-13.5 (1.1)	-17.3 (1.2)	0.0024
Urinary volume / void (mL)		(N = 300)	(N = 290)	
Mean Baseline	0	155.9 (3.0)	151.0 (2.9)	
Mean Change from Baseline	1	12.1 (2.1)	21.6 (2.8)	0.0036
	4	17.2 (2.5)	30.0 (3.1)	0.0007
	12	18.9 (2.8)	29.8 (3.2)	0.0039

Figure 1: Study 018, Mean change from Baseline in Urinary Frequency/24 hours by visit

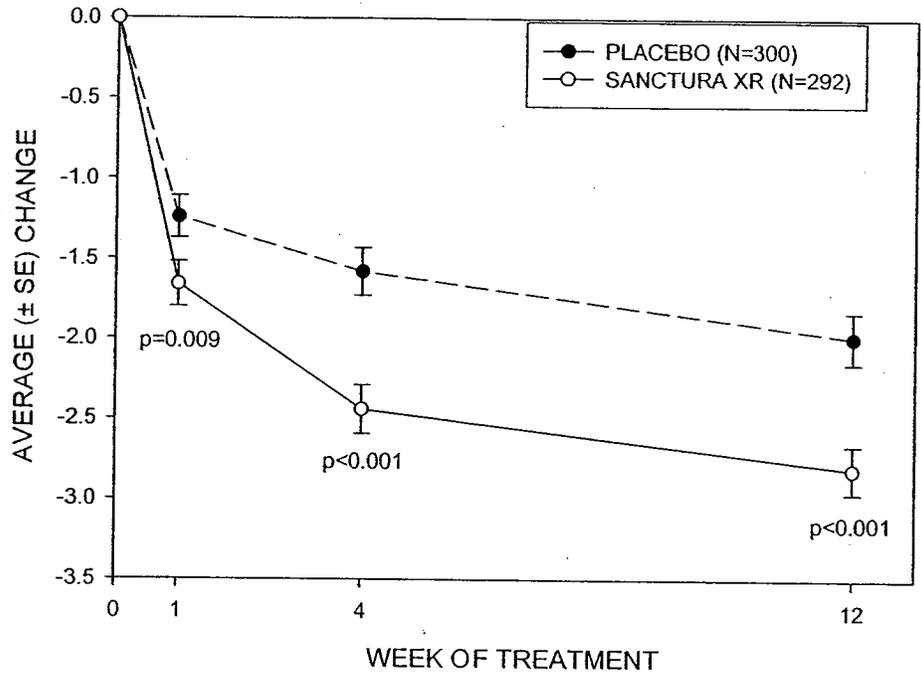
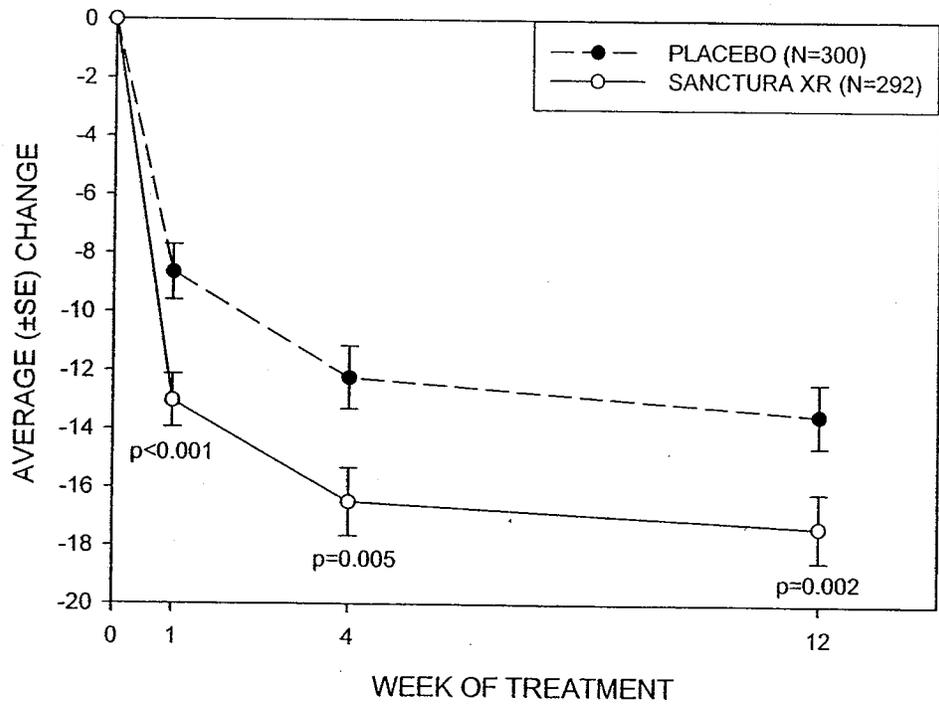


Figure 2: Study 018, Mean change from Baseline in Incontinence Episodes /Week by visit



Study 2 included 543 patients in both SANCTURA XR 60 mg and placebo groups and was identical in design to Study 1. As illustrated in Table 2 and Figures 3 and 4, SANCTURA XR

demonstrated statistically significantly ($p < .01$) greater reductions in urinary frequency and incontinence episodes, and increases in void volume when compared to placebo at Weeks 4 and 12. However, at Week 1, statistically significant improvements were seen only in urinary incontinence episodes and volume void.

Table 2: Summarized Efficacy Results for Study - 022

Mean Change from Baseline in Urinary Frequency, Urge Incontinence Episodes and Volume Void

Efficacy Endpoint	Week	Placebo (N = 276)	SANCTURA XR (N = 267)	P-Value
Urinary frequency / 24 hours				
Mean Baseline	0	12.9 (0.2)	12.8 (0.2)	
Mean Change from Baseline	1	-1.2 (0.2)	-1.4 (0.2)	0.0759
	4	-1.7 (0.2)	-2.3 (0.2)	0.0047
	12	-1.8 (0.2)	-2.5 (0.2)	0.0009
Urge incontinence episodes / week				
Mean Baseline	0	28.3 (1.4)	28.2 (1.2)	
Mean Change from Baseline	1	-7.3 (1.0)	-11.9 (1.0)	<0.0001
	4	-10.6 (1.1)	-15.8 (1.1)	<0.0001
	12	-11.3 (1.2)	-16.4 (1.3)	<0.0001
Urinary volume / void (mL)				
Mean Baseline	0	151.8 (2.8)	149.6 (2.9)	
Mean Change from Baseline	1	11.9 (2.5)	24.1 (2.4)	<0.0001
	4	19.6 (3.1)	29.3 (3.0)	0.0020
	12	17.8 (3.3)	31.5 (3.4)	0.0014

Figure 3: Study - 022, Mean change from Baseline in Urinary Frequency/24 hours by visit

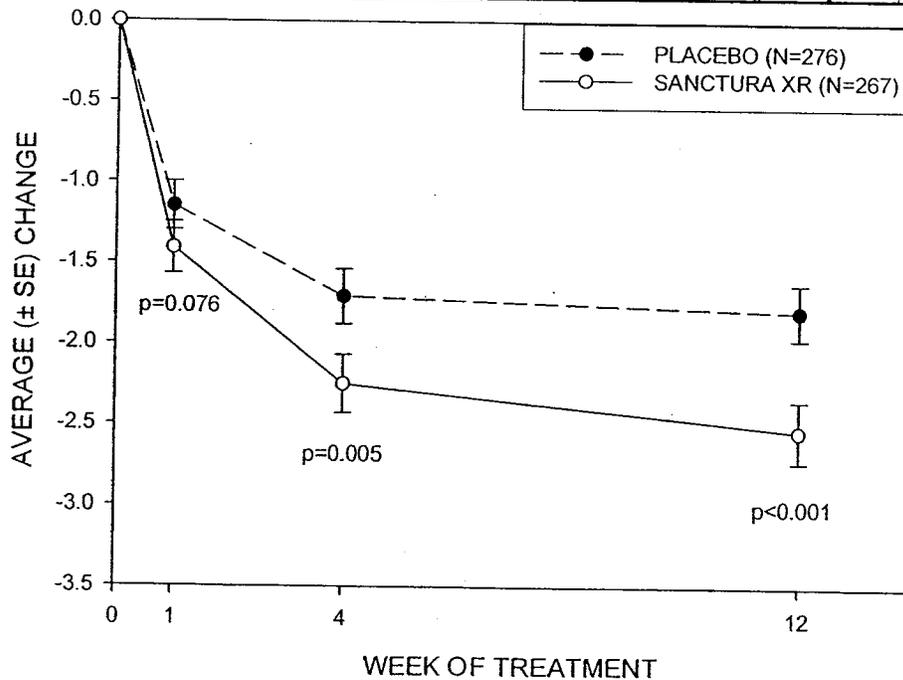
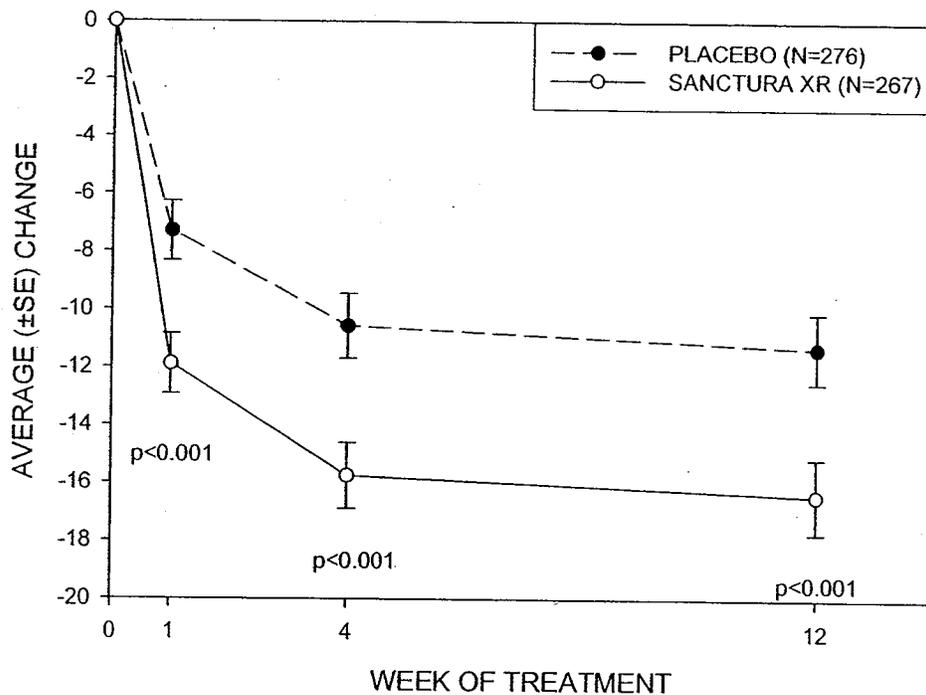


Figure 4: Study - 022, Mean change from Baseline in Incontinence Episodes /Week by visit



Reviewer's comments:

1. The consistency of the findings across both Phase 3 trials in the primary and key secondary endpoints provides firm support for the efficacy conclusions for this application.
2. In Study -018, Sanctura XR 60mg produced significantly ($p < .01$) greater reductions in the urinary frequency and incontinence episodes and increases in void volume when compared to placebo starting at week 1 and maintained through weeks 4 and 12.

In Study - 022, Sanctura XR demonstrated statistically significantly ($p < .01$) greater reductions in urinary frequency and incontinence episodes, and increases in void volume when compared to placebo at weeks 4 and 12. However, at week 1 statistically significant improvements were seen in urinary incontinence episodes and volume void only.

4.2 Clinical Safety

4.2.1 Extent of Exposure/Overview

Safety data was primarily drawn from a total of 1165 subjects enrolled in 2 completed pivotal studies in the U.S. Overall, 769 and 238 patients received treatment with SANCTURA XR for at least 24 and 52 weeks, respectively. The safety evaluation in this large database is adequate and meets the ICH guidance unto itself for the number of subjects exposed to Sanctura XR and for the duration of exposure. Furthermore, the previous safety database that supported the approval of SANCTURA immediate release in 2004 was quite extensive, and it is clear that the maximum serum concentrations of the modified-release XR formulation are lower than those for the immediate release (IR) formulation.

Sanctura XR was well tolerated in the clinical studies supporting this NDA. The reported adverse events, such as dry mouth, constipation, dry eyes, abdominal pain, dyspepsia, urinary tract infection (UTI), urinary retention, headache and nasopharyngitis, are primarily those related to the drug's anticholinergic properties and are consistent with the known side effects of other approved anticholinergic compounds used to treat OAB. No significant cardiovascular, hepatic, renal, or hematologic toxicities were identified.

However, **Sanctura XR** is not recommended for use in patients with severe renal insufficiency. Trospium chloride is excreted by the kidneys. As previously demonstrated in a dedicated special population study using SANCTURA IR in patients with severe renal insufficiency (creatinine clearance <30 ml/minute), severe renal insufficiency was associated with a 2-fold increase in C_{max} and a 4.5-fold increase in mean AUC relatively to healthy subjects. Based upon this degree of alteration in the disposition of trospium chloride and the potential increased risk of adverse reactions, SANCTURA XR is not recommended for use in patients with severe renal insufficiency. In regard to lesser degrees of renal insufficiency, the pharmacokinetics of Sanctura XR were not specifically studied in people with moderate or mild renal insufficiency in dedicated special population trials. However, the population PK dataset for the pivotal Phase 3 study -018 included PK data from 115 patients with mild renal insufficiency (creatinine clearance 50-80 ml/minute), and 30 patients with moderate renal impairment (creatinine clearance 30-50 ml/minute). Analyses of these data did not suggest a clear impact of this degree of renal insufficiency on trospium steady-state concentrations.

The sponsor also conducted EKG safety assessment from the pivotal studies - 018 and - 022 that indicated comparable changes in the PR, QRS, and QT intervals from baseline to endpoint between placebo and treatment groups that were regarded as not clinically meaningful. The change in mean pulse from baseline to endpoint was 0.1 bpm and 2.8 bpm for subjects in the placebo and trospium groups, respectively.

The sponsor has previously conducted a "thorough QT study" (TQT) for trospium chloride (Sanctura immediate release) that showed no significant change in corrected QT interval in normal healthy volunteers in a moxifloxacin and placebo-controlled setting. This study included trospium chloride in therapeutic and in supra-physiological doses.

Reviewer's comment: The controlled safety database for Sanctura XR is adequate by current ICH guidelines. The long-term safety data (6 months and 1 year) is from U.S controlled trials. Most adverse events with Sanctura XR were anticholinergic side effects, and these were likely to be seen within 2 weeks of initiating the therapy.

4.2.2 Deaths, Serious Adverse Events (SAEs) and Discontinuations Due to AEs

4.2.2.1 Deaths

There were **no deaths** in either randomized, placebo-controlled, Phase 3 study (Study - 018 and Study - 022).

However, there were **three subjects who died** during the open label treatment phase. Two subjects died from causes judged by the investigator to be unrelated to the study medication, and while the cause of the third death is unconfirmed at this time, the subject apparently died from complications of a preexisting gynecologic cancer. Brief narratives for these 3 subjects are provided below:

Subject 261-3355 was a 48-year old white female who had been randomized to active study medication in the double-blind study phase. She was first treated with Sanctura XR on _____. Her past medical history was significant for seasonal allergies, lower back and bilateral knee pain, tension headaches and depression. She was taking Flonase and Allegra PRN since 2000 for her allergies and Desogen since 2003 for birth control. On _____ (193 days following her first dose of study medication), the subject experienced a pulmonary embolism. An autopsy was performed and the cause of death was pulmonary thrombo-embolism. The event was judged by the investigator to be definitely not related to study medication.

Subject 035-6400 was a 54-year old white female who had been randomized to active study medication in the double-blind study phase. She was first treated with Sanctura XR on _____. Her past medical history includes hypothyroidism since 1988 treated with daily synthroid replacement and post-menopause since 2000. She had been taking Triest and progesterone gel since 2000. The subject had a history of abnormal stress tests. On _____ (143 days following her first dose of study medication), the subject experienced a series of events, including a left internal carotid artery occlusion, hypertension, an acute cerebral infarct (a stroke in the middle cerebral artery territory), and a brain stem herniation. The subject died the next day on _____ because of the herniation. All events were judged by the investigator to be definitely not related to study medication.

Subject 241-3688 was an 84-year old white female who had been randomized to placebo in the double-blind study phase. She was first treated with Sanctura XR on _____. The subject had a medical history of colon cancer, hypertension, seasonal allergies, transient ischemic attack in 2005, hysterectomy, ovarian cyst, bladder sling, arthritis, and hypothyroidism. She had been taking aspirin, benicar, Protonix, synthroid, and fish oil. On _____ (167 days following her first dose of active study medication), the subject was diagnosed with metastatic gynecologic malignancy to the right chest peritoneum (malignant pleural effusion), presumed ovarian, for which she received chemotherapy. The event was considered resolved with sequelae and judged by the investigator to be definitely not related to study medication. On _____ (179 days following her first dose of active study medication), the subject experienced a pulmonary embolism, which was considered resolved with sequelae and judged by the investigator to be definitely not related to study medication. The subject withdrew from the study on November 30, 2006, citing that her chemotherapy would be very involved over the next several months. Although she returned her study medication, she was not seen for the early termination visit. The subject had died on _____. The study site obtained the certificate of death which indicated that the cause of death was metastatic cancer of unknown primary origin.

4.2.2.2 Serious adverse events

At the time of the original NDA submission, in all placebo-controlled trials of Sanctura XR 60mg daily, a total of 10 (1.7%) placebo subjects and 8 (1.4%) Sanctura-XR subjects experienced at least 1 new-onset SAE. The SAEs in the eight (8) Sanctura XR-treated subjects included ischemic stroke in 2 subjects, and one subject each with: B-cell lymphoma, "biliary dyskinesia", duodenal ulcer hemorrhage, upper limb fracture, pneumonia aspiration, pulmonary sepsis, and small bowel obstruction. **None** of these serious adverse events (SAE) were judged as being at least possibly related to the study drug by the investigators.

A total of 35 (4.6%) subjects experienced at least 1 new-onset SAE during the open-label treatment phase. The SAEs reported in 2 or more subjects in this open-label phase were: non-cardiac chest pain (3, 0.4%), cerebrovascular accident (2, 0.3%), lumbar spinal stenosis (2, 0.3%), nephrolithiasis (2, 0.3%) and pulmonary embolism (2, 0.3%). No other SAE was reported in more than 1 subject. **None** of these SAE's was judged to be at least possibly related to study medication by the investigators. There were 2 serious gastrointestinal system events, each reported in 1 subject: ulcerative colitis and gastroesophageal reflux disease. There were no reports of serious constipation or other gut motility-related event, nor any serious events of urinary retention.

4.2.2.3 Discontinuations due to adverse events

At the time of the original NDA submission, the reported discontinuations due to adverse events (AEs) were as follows:

For **Study – 018**, there were a total of 11 (3.6%) placebo subjects and 12 (4.0%) Sanctura-XR subjects who discontinued treatment due to an adverse event. The events that led to discontinuation in the 12 Sanctura XR-treated subjects included urinary retention and dry mouth in 2 subjects each, and the following events reported in 1 subject each: rash, nasal dryness, flatulence, dyspepsia, chest wall pain, "biliary dyskinesia", abdominal pain, abdominal discomfort, and "faecaloma". The incidence of discontinuation due to commonly reported anticholinergic AEs of constipation, dry mouth and urinary retention were 1 %, , 0.7 %, and 0.7 %, respectively, in the Sanctura XR group; and there were no discontinuations for these AEs in the placebo group.

For **Study – 022**, there were a total of 8 (2.8%) of placebo subjects and 18 (6.4%) Sanctura-XR subjects who discontinued treatment due to an adverse event. The events that led to discontinuation in the 18 Sanctura XR-treated subjects included constipation in 3 subjects, dry mouth, headache, upper abdominal pain, and ischemic stroke in 2 subjects each, and the following events reported in 1 subject each: urinary retention, small intestinal obstruction, renal pain, non-cardiac chest pain, nausea, loose stools, hypertension, flatulence, dyspnea, dry throat, dry skin, dry eye, constipation aggravated, back pain, abdominal pain, and abdominal distension. The incidence of discontinuation due to commonly reported anticholinergic AEs of constipation, headache, dry mouth, upper abdominal pain, and urinary retention were 1.1 %, 0.7 %, 0.7 %, and 0.4%, respectively, for the Sanctura XR group. In the placebo group, there were no discontinuations due to dry mouth, upper abdominal pain, or urinary retention, and one patient each discontinued due to headache (0.4%) and constipation (0.4%).

For the **Open – Label treatment phase**, a total of 22 (2.9%) subjects experienced a TEAE that resulted in discontinuation. TEAE's that resulted in premature discontinuation in more than one subject were: dry mouth (4 subjects, 0.5%) and constipation (2 subjects, 0.3%). In addition, there was 1 subject who discontinued due to aggravated constipation (did not require any further medical intervention), and one other who discontinued due to abdominal pain that was mild.

Reviewer's comment: The incidence and type of serious adverse events that lead to discontinuation are consistent with Sanctura XR's pharmacological action as a potent, non-selective anticholinergic. In the opinion of this medical TL/reviewer, the incidence rates and types of serious adverse events (and discontinuations due to adverse events) are acceptable in view of the treatment effect of Sanctura XR. It is notable that the incidence of commonly reported anticholinergic adverse events such as dry mouth and constipation were lower for Sanctura XR in this NDA as compared to those reported for Sanctura 20mg twice daily dosing in the NDA approved in May 2004.

4.2.2.4 Overall adverse events

In this reviewer's opinion, the overall adverse event terms and incidences from the two, randomized, placebo-controlled, U.S., Phase 3, OAB trials (Studies – 018 and – 022) provide the clearest evidence for the overall, commonly reported adverse reactions and safety profile with Sanctura XR.

In these two studies combined, the AE's are presented below in Table 3 *irrespective of investigator's assessment of relationship to study drug*. The most commonly reported treatment-emergent adverse events (TEAEs) were: dry mouth, constipation, urinary tract infections, and headache. Dry mouth and constipation were most often reported within the first week of treatment. Other adverse events of note, reported by more than two subjects, and at a higher incidence in the Sanctura XR group than the placebo group included: dry eyes, rash, tachycardia, urinary retention, and blurred vision. A summary of reported TEAEs of interest is shown below:

Table 3: TEAE's of Interest in Studies – 018 and - 022 combined, irrespective of investigator's judgment on causality.

Preferred Term	Sanctura XR N=578	Placebo N=587
Dry mouth	64 (11.1)	22 (3.7)
Constipation	52 (9.0)	10 (1.7)
Urinary tract infection	42 (7.3)	29 (4.9)
Headache	19 (3.3)	21 (3.6)
Nasopharyngitis	17 (2.9)	10 (1.7)
Nausea	15 (2.6)	16 (2.7)
Upper respiratory infection	13 (2.2)	23 (3.9)
Influenza	13 (2.2)	9 (1.5)
Diarrhea	11 (1.9)	14 (2.4)
Dry eye	10 (1.7)	3 (0.5)
Rash	7 (1.2)	2 (0.3)
Tachycardia	6 (1.0)	3 (0.5)
Urinary retention	5 (0.9)	2 (0.3)
Blurred vision	4 (0.7)	2 (0.3)
Dizziness	3 (0.5)	9 (1.5)
Ischemic stroke	2 (0.3)	0 (0.0)
Myocardial ischemia	1 (0.2)	1 (0.2)
Prolonged QT	1 (0.2)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.2)

When these adverse events are analyzed taking into consideration the investigator's judgment on causality, the overall safety profile is consistent, although the actual number of events are fewer and the differences between treatment groups is smaller.

In regard to the overall AE's that occurred during **Open Label phase** treatment, the anticholinergic adverse events that occurred with the highest incidence during the Open-Label phase were constipation and dry mouth. All constipation events were judged as mild or moderate in severity. There was one report of a subject with severe dry mouth, while the remaining reports of dry mouth were judged to be either mild or moderate in severity. New-onset dry eyes was reported for 2 subjects during the Open-Label phase (both events were judged as mild and possibly related to study medication) and there were 7 reports of rash (1 of which was judged as possibly related to study medication). Urinary retention was reported in 5 patients, and each of these events was reported to be at least possibly related to study medication. Two of the urinary retention events were judged to be severe by the investigator but required no further medical intervention.

In regard to other clinically relevant AE reports in the Open-Label phase treatment, there were no reports of severe headache or severe dizziness. Cardiac-related events were rare. Gut motility events were the most common events of interest that started during Open-Label phase, with constipation being the most frequent. Other gut motility events (eg, abdominal discomfort, abdominal distension, and abdominal pain) were rarely reported. The majority of constipation events were judged to be mild in severity and at least possibly related to study treatment, and no constipation event was judged to be severe. There were 5 reports of aggravated constipation (from subjects who had a medical history of constipation prior to entry into the study), each of which was judged to be at least possibly related to study treatment. One of these reports of aggravated constipation was judged to be severe, but did not require hospitalization.

Only 3 subjects reported having one or more UTI judged by the investigator as at least possibly related to treatment. All other subjects with UTI's had the causal relationship assessed as remote or definitely not related to the study medication (causal relation was judged by the investigator). There was 1 severe UTI reported, while the remaining reports were judged to be mild or moderate in severity.

There are no new adverse events reported after long-term use. The incidences of most reported adverse events in 12-week studies did not change markedly with prolonged use. Table 4 shows the incidence of adverse events in open-label studies judged to be at least possibly related to treatment and in at least 1% of patients.

Table 4: Incidence of open-label treatment emergent adverse events reported in at least 1% of patients judged at least possibly related to treatment

MedDRA Preferred term	Number of patients (%)	
	6 Months Exposure to SANCTURA XR N = 769	12 Months Exposure to SANCTURA XR N = 238
Dry mouth	34 (4.4)	6 (2.5)
Constipation	35 (4.6)	5 (2.1)

Reviewer's comment: The overall adverse event profile is consistent with the pharmacological effect of trospium chloride as a potent and non-selective anticholinergic agent. In the opinion of the reviewer, the types of adverse reactions reported and their incidences are generally acceptable in view of the treatment effect of Sanctura XR. There were no unexpected or surprising adverse events reported with Sanctura XR.

4.2.5 Other potential safety issues

4.2.5.1 Relationship of age to reported adverse events

The clinical review team analyzed the adverse events reported in Studies -018 and -022 by subject age (< 65 years, 65-75 years, and >75 years) and by treatment group. In the opinion of this reviewer, several adverse reactions were reported at a higher incidence in Sanctura XR subjects ages 65 and over as compared to younger subjects (See Table 5 below). These included: dry mouth, constipation, abdominal pain, dyspepsia, urinary tract infection and urinary retention.

In addition, falls were reported in 3 patients aged 75 and over. In all 3 patients, the adverse event was reported following at least 70 days of treatment with Sanctura XR. While the source documents described a clear alternative reason for fall in 2 patients, the relationship of Sanctura XR to the event could not be excluded in 1 patient. In addition, in all 3 events, the investigator judged the fall to be not related to treatment.

Table 5: Incidences of reported anticholinergic adverse events by patient age in Phase 3, controlled clinical trials, irrespective of investigator's judgment on causality.

	<65 years n=352	65-74 years n=141	≥75 years n=85
Dry mouth	9.7%	14.9%	10.6%
Constipation	6.3%	14.9%	10.6%
Dyspepsia	0.9%	3.5%	2.4%
Abdominal Pain	1.1%	5.0%	0%
UTI	3.7%	12.1%	14.1%
Urinary retention	0.3%	1.4%	2.4%

From the Table above, it is clear that the incidences of commonly reported (and apparently anticholinergic-related) adverse events is higher in patients aged 75 years and older. This does not appear to be related to differences in steady-state plasma trospium concentrations, as may be seen in the clinical pharmacologist's primary review. Therefore, it is assumed that this difference reflects an enhanced sensitivity to anti-muscurinic agents in this particular subgroup. Due to small sample size, definitive statistical comparisons between groups cannot be made.

Reviewer's comment: The proposed labeling was revised to reflect these findings in the Geriatric Use section.

4.2.5.2 Gender-related safety issues

Data from healthy subjects suggests lower systemic trospium exposure in males compared to females after dosing with Sanctura XR. The Phase 3 study population was predominantly female (83.5%). In this limited male population, there were no apparent reduction in effectiveness, and similarly, the safety in women was demonstrated to be adequate by standard clinical parameters.

4.2.5.2 Cardiovascular effects including vital signs and ECGs

There were no serious cardiovascular adverse events reported in causal association with Sanctura XR. ECG's were analyzed, including data for PR, QRS and QTcF interval changes from baseline. No changes were reported between the treatment groups. However, there were differences between Sanctura XR and placebo groups in the changes from baseline in mean heart rate. These demonstrated a Sanctura XR-related increase in mean heart rate of approximately 3-4 beats per minute over placebo.

There was no evidence of QT prolongation with both therapeutic and supra-therapeutic doses of trospium chloride as demonstrated in a thorough QT study (TQT) conducted for the previous approval of Sanctura 20mg BID in 2004.

Reviewer's comment: In the opinion of this medical TL/reviewer, a slight increase in the mean heart rate is an expected adverse event for the anticholinergic class and does not pose a significant safety concern.

4.2.5.3 Any other potential safety issues

There was no evidence of any Sanctura XR effect on laboratory parameters.

All traditional precautions that pertain to systemic anticholinergic medications also pertain to Sanctura XR. These include caution when using the drug in patients with bladder outlet obstruction, with slow gastrointestinal motility, and with glaucoma. Further, caution must be used to avoid heat prostration, when ingesting alcohol, and when taking other medications that have anticholinergic effects.

Of note, dissolution of the modified-release Sanctura XR was shown to be enhanced in the presence of high concentrations of alcohol. Therefore, in consultation with our Clinical Pharmacology colleagues, it was determined that alcohol should not be consumed for up to two hours after administration of Sanctura XR to preclude "dose-dumping".

5. Major issues from other disciplines

5.1 Clinical pharmacology

The following major clinically relevant issues were of importance during the extensive and detailed clinical pharmacology review as finalized by Dr. Apparaju:

In regard to use in patients with renal insufficiency (RI): Sanctura XR is not recommended for use in patients with severe renal insufficiency (creatinine clearance <30ml/minute). The pharmacokinetics of Sanctura XR in patients with severe renal insufficiency has not been evaluated. While sufficient steady-state average concentrations were available for those patients with mild and moderate RI, only 4 subjects with severe RI contributed data. Considering the known metabolic pathway for trospium, as well as the previous increase in C_{max} and AUC seen in severe RI patients given Sanctura IR, it was determined that Sanctura XR should not be recommended for use in severe RI.

In regard to use in patients with hepatic impairment: Because the overall exposure from once daily Sanctura XR 60mg is lower relative to the approved 20mg BID formulation, no dosage adjustment is recommended for Sanctura XR in presence of hepatic impairment. Caution is

advised, however when administering Sanctura XR to patients with moderate to severe hepatic impairment.

In regard to interaction potential with alcohol: Based upon dissolution results showing enhanced dissolution of Saanctura XR in high concentration alcohol media, it was determined that alcohol should not be consumed within 2 hours of Sanctura XR administration.

In regard to interaction potential with antacids: Results from a study evaluating the effect of antacid containing aluminum hydroxide and magnesium carbonate on trospium pharmacokinetics from Sanctura XR showed that average systemic exposure to trospium was comparable with and without antacid. However, several subjects showed either an increase or decrease in trospium concentrations. The clinical relevance of these findings is unknown.

In regard to interaction potential with food: Administration of Sanctura XR immediately after a high fat content meal reduced the bioavailability of trospium chloride by 35% for AUC and by 60% for Cmax. It is therefore recommended that Sanctura XR be taken on an empty stomach at least one hour before a meal. It is notable that the clinical studies were conducted in the same manner as the labeling advises use – one hour before a meal.

In regard to gender effect on PK: As previously stated in the Clinical safety section, data from healthy subjects suggests lower exposure in males compared to females. However, the available efficacy data in men does not reveal reduced effectiveness, and the safety data in women is substantive and supportive of approval.

In regard to race: While formal pharmacokinetic differences due to race have not been studied, the clinical studies included all-comers, including White, Black and Hispanic subjects, without evidence of clinical differences in effectiveness or safety.

In regard to age: In the phase 3 clinical trial of Sanctura XR, the observed plasma trospium concentrations were similar in older (>65 years) and younger (<65 years) OAB patients. The reader is referred to the Clinical Safety section in regard to the relationship of adverse events to age.

In regard to pediatric studies: The pharmacokinetics of Sanctura XR were not evaluated in pediatric patients. Based upon the _____, the Sponsor will be offered a waiver of pediatric studies under PREA.

Reviewer's comment: All clinically relevant comments from Clinical Pharmacology review team have been acknowledged and those that required regulatory action have been resolved.

5.2 Chemistry, manufacturing and controls

According to Dr. Holbert's final review, all chemistry related issues have been resolved except for final container (bottle) and carton labeling. In conjunction with DMETS, the Chemistry team will finalize the container/carton labeling prior to the final action. However, there appear to be no outstanding issues that would preclude approval of Sanctura XR.

5.3 Biometrics

According to Dr. Sobhan's final review, from a statistical perspective, the application provided adequate data to support the efficacy of Sanctura XR 60mg in the treatment of overactive bladder symptoms.

The statistical analysis showed that compared to placebo, Sanctura XR was statistically significantly ($p < .01$) better than placebo in treating patients with symptoms of OAB, as indicated by the improvements from baseline to weeks 4, and 12 in the two co-primary endpoints: change in average daily toilet voids and average daily urge urinary incontinence episodes, and in key secondary end point: change in voided volume in one pivotal study. In a second pivotal study, statistically significant differences from placebo were seen as early as Week 1.

5.4 Pharmacology/Toxicology

The final PharmTox review by Dr. McLeod-Flynn stated that:

“There are no impediments to approval of this application from a pharmacology/toxicology perspective.”

5.5 Financial Disclosure

Review of financial certification information by the primary medical officer revealed that the sponsor complied with 21 CFR 54; i.e., there was no disclosure of financial interests that could bias the outcome of the trials under NDA 22-103.

5.6 OSE/DSRCS (Division of Surveillance, Research and Communication Support)

It is the understanding of this reviewer that the revised Patient Information section of the FPI submitted to the office of DSRCS is acceptable from the patient comprehension perspective as per the review team in the Division of Surveillance, Research and Communication Support.

5.6 Division of Medication Errors and Technical Support (ODS/DMETS)

DMETS spent considerable time and effort reviewing the Sponsor's proposed tradenames including Sanctura Q, Sanctura CR and finally, Sanctura XR. DMETS has no objection to the use of the proprietary name, Sanctura XR. However DMETS recommended container and carton labeling recommendations to enhance the differences between Sanctura and Sanctura XR and also advise that Sponsor institute an “educational program” to practitioners with product launch to minimize confusion with Sanctura. These recommendations were conveyed to Sponsor who accepted the need for an “educational program” of this sort. Further, the Sponsor made the requested revisions to container/carton labeling and these are under final review at this time.

5.7 Division of Drug Marketing, Advertising and Communications (DDMAC)

The clinical review team carefully assessed each and every comment in the DDMAC review and made all appropriate and clinically relevant changes to the label. Based upon our labeling discussions with Sponsor, all these items were taken into consideration and resolved.

Regulatory summary: At this time, I recommend that Sanctura XR 60 mg should be granted a marketing approval for the OAB indication. There remain no outstanding issues that preclude approval.

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this page is the manifestation of the electronic signature.**

/s/

Suresh Kaul
7/27/2007 05:17:39 PM
MEDICAL OFFICER

Mark S. Hirsch
7/27/2007 05:26:27 PM
MEDICAL OFFICER

I concur. See my brief Deputy Director's memo to
follow the finalization of all labeling.

MEDICAL OFFICER'S REVIEW (DRAFT)

NDA 22-103 SANCTURA XR (trospium chloride)

Application Information

NDA # 22-103
Sponsor Indevus Pharmaceuticals, Inc.
Primary Efficacy Studies: IP631-018, IP631-022,
Submission Date: October 13, 2006
PDUFA Goal Date: August 13, 2007
Review Status: Standard

Generic Name Trospium chloride
Proposed Trade Name Sanctura XR

Drug Categorization:
Pharmacological Class Anticholinergic
Proposed Indication Treatment of Overactive Bladder (OAB)
Proposed Dose Regimen 60mg daily (AM)
Strength and Dosage Form 60mg extended release capsules
Route of Administration Oral

Reviewer Information:
Clinical Reviewer Harry Handelsman, DO
Acting Medical Team Leader Suresh Kaul, MD, MPH
Acting Deputy Director Mark Hirsch, MD
Division Director Scott Monroe, MD

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I. Executive Summary

1. Conclusions and Recommendation:

In the opinion of this reviewer, the evidence presented in the submission of this NDA is adequate in support of the safety and effectiveness of Sanctura XR, and from a clinical perspective, Sanctura XR taken once daily **should be approved** for the indication **“treatment of overactive bladder (OAB) symptoms”** in patients with urinary frequency, urinary urge incontinence (UUI), and other related symptoms associated with OAB, in men and women 18 years of age and older.

2. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

Trospium is a quaternary ammonium derivative of tropine with anticholinergic properties and predominant peripheral muscarinic like activity that antagonizes the effect of acetylcholine and exhibits parasympatholytic action which, in the lower urinary tract, enables detrusor relaxation and subsequent inhibition of bladder evacuation, leading to enhanced bladder compliance with increased capacity and control.

In support of this **NDA 22-103**, the sponsor submitted data from 2 pivotal Phase-3 trials (**IP631-018 and IP631-022**) involving 1165 subjects at 117 U.S. study sites. In addition, this NDA submission includes data from 3 Phase-1 pharmacokinetic studies (82 subjects) and a single Phase-2 study (148 subjects). The focus was put primarily on the study reports from the 2 pivotal phase-3 trials.

The design of the 2 pivotal studies was similar. The only meaningful difference in the studies was the inclusion of a population PK study in study -018. This allowed for an integration of the clinical databases for analyses. Both studies were double-blind, randomized, placebo-controlled and conducted for 12 weeks with an optional 9-month open-label extension. Study -018 enrolled 601 subjects at 55 sites, and Study -022 enrolled 564 subjects at 62 sites. The inclusion and exclusion criteria, and the criteria for evaluation were the similar for both studies.

The objectives were to evaluate the effects of once daily dosing of Sanctura XR compared to placebo on urinary frequency, UUI, and other related symptoms associated with OAB with predominant UUI over a 12 week treatment period.

B. Efficacy

The **co-primary efficacy variables** for the pivotal studies, based on urinary diary data collected over 3 days prior to baseline and at the end of Weeks 1, 4, and 12 were:

- The change in average number of toilet voids/day.
- The change in UUI episodes frequency/day.

Secondary efficacy variables, also based on urinary diary data were:

- UUI episode frequency.
- Urinary severity associated with toilet voids measured by the IUSS.
- OAB Symptom Composite Score/day.
- Volume voided /toilet void collected for 2 days.
- Urge frequency/day.
- “Dry rate” for UUI outcome defined as no UUI episodes.
- Stress incontinence episodes frequency/day.
- Total incontinence episodes frequency/day.
- Normal void frequency outcome, defined as average of ≤ 8 toilet voids/day.
- Complete responder rate outcome, defined as an average of ≤ 8 toilet voids/day and no UUI episodes/day.

The study results provide substantial evidence in support of effectiveness of Sanctura XR for the treatment of patients 18 years and older with symptoms of OAB.

The efficacy conclusions in the pivotal studies were as follows:

- Sanctura XR showed an improvement in toilet voids (urinary frequency) at week 12 in both trials. Statistical significance was achieved in both pivotal trials at the $p < 0.0001$ level. The average reduction of toilet voids was from 12.8/day at baseline to 10.1/day at week 12. **The treatment effect was observed as early as Week 1.**
- Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in the average number of UUI episodes /day at Week 12 (4.1 UUIs/day at baseline to less than 1.7 UUIs/day at Week 12).
- Sanctura XR demonstrated statistically significant greater improvements in urgency severity and volume voided.
- Sanctura XR also demonstrated a significant improvement in other clinically relevant secondary endpoints in the studies reviewed.
- There was no subgroup identified that had a meaningful better or worse relative efficacy outcome than other subgroups, and each group assessed, demonstrated a positive effect for each of the primary and secondary efficacy parameters.

Reviewer's Comment: In the opinion of this reviewer, the effect of Sanctura XR is well supported by results from the controlled clinical trials.

C. Safety

In this medical officer's review, safety data is primarily drawn from a total of 1165 subjects enrolled in 2 completed pivotal studies in the U.S. The safety evaluation in this large database is adequate and meets the ICH guidance for the number of subjects exposed to Sanctura XR and for the duration of exposure. QT safety assessment from the pivotal studies -018 and -022 indicated comparable changes in the PR, QRS, and QTcF from baseline to endpoint between placebo and treatment groups that were regarded as not clinically meaningful. The change in mean pulse from baseline to endpoint was 0.1 bpm and 2.8 bpm for subjects in the placebo and trospium groups, respectively, and were consistent with changes noted during the trospium 20mg BID Phase-3 studies.

Sanctura XR was well tolerated in these studies, and no clinically meaningful treatment differences were noted between gender, race, or age subgroups. The reported significant adverse events are primarily those related to known side effects of other approved anticholinergic compounds used to treat OAB (including trospium 20mg BID). No significant cardiovascular, hepatic, renal, or hematologic toxicities were identified.

Safety-related Findings:

Treatment-related-adverse-events (TEAEs) reported in $\geq 1.5\%$ of subjects were dry mouth (3.7% placebo, 10.7% Sanctura XR), constipation (1.5% placebo, 8.5% Sanctura XR), dry eye (0.2% placebo, 1.6% Sanctura XR), flatulence (0.5% placebo, 1.6% Sanctura XR), and headache (2.4% placebo, 1.4% Sanctura XR). Study medication was permanently discontinued due to TEAEs in 3.2% of placebo and 5.2% of Sanctura XR groups.

There were **no deaths** in either study groups, and **no Serious Adverse Event (SAE)** was judged as being at least possibly related to study drug.

Both constipation and dry mouth were usually reported within the first week of treatment, and together with other expected TEAEs were slightly higher in the Sanctura XR than placebo groups.

The incidence of nervous system and cardiac disorders were similar between the treatment groups.

The mean and median changes from baseline to endpoint were small, deemed clinically insignificant, and were generally similar for all laboratory parameters.

Changes in blood pressure from baseline to endpoint were similar between treatment groups. The Sanctura XR group demonstrated a higher mean increase in pulse rate compared with placebo.

The ECG recordings that including QTcF changes from baseline to endpoint were comparable between treatment groups (except for a small increase in heart rate that was consistent with changes in pulse rate observed in the Sanctura XR group). Physical examinations otherwise were unremarkable.

D. Dosing

The 60mg dose of Sanctura was selected based on results from both Phase-1 and Phase-2 studies. The pivotal studies expanded on the safety and efficacy results, assessing once daily dosing in the morning or evening. Sanctura XR given at a dose of 60mg daily was determined to be the maximally tolerated and effective dose by sponsor in improving the symptoms of OAB, and the morning-treatment group had a slightly more desirable safety profile.

E. Special Populations

Effect of age, gender and race:

There were no clinically meaningful differences between treatment groups with respect to incidence of adverse events (AE's) by age or race subgroups.

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II. Integrated Summary of Efficacy (ISE)

A. Brief Statement of Conclusions

Both the pivotal studies **IP631-018** and **IP631-022** were adequate and well-controlled studies conducted in the US. Both provide substantial evidence of efficacy of Sanctura XR in the primary and secondary efficacy variables.

The improvement in the signs and symptoms of overactive bladder (OAB) is supported by data suggesting an associated improvement in health-related quality of life assessments.

The proposed indication, therefore, is well supported by the efficacy data.

B. Method of Efficacy Review

The reviewer's basic approach to the efficacy review involved:

- Review of the proposed indication, protocols, regulatory and scientific background.
- Identification and review of well-controlled studies to support the indication.
- Review of each study for efficacy.
- Generate conclusions regarding efficacy from the pivotal and supporting studies.

C. List of Studies, Designs, Population and Efficacy Variables

The following studies were analyzed in detail during the review process:

- IP631-018 - a Pivotal study, Phase-3
- IP631-022 - a Pivotal study, Phase-3
- IP631-011 - a Supporting Study, Phase-1
- IP631-019 - a Supporting Study, Phase-1
- IP631-020 - a Supporting Study, Phase-1
- IP631-016 - a Supporting Study, Phase-2

The 2 pivotal trials were randomized, multi-center, double-blind, placebo-controlled, parallel group studies of efficacy and safety conducted in the US for a term of 12 weeks. There was an optional 9-month open label extension.

Both studies collected urinary data, derived from urinary diaries, on toilet void frequency, the urgency severity associated with each toilet void, and the number of incontinence episodes for 3 days prior to the baseline, and at weeks 1, 4, and 12 visits. Data for volume voided was collected for 2 days prior to these visits.

Key study entry criteria for the pivotal trials included:

1. Males and females 18 years and older.
2. Symptomatic OAB for \geq than 6 months.
3. Average \geq 10 toilet voids/day and at least 1 "severe" urgency severity rating/3 days as measured by the IUSS.
4. Minimum of 3 UUI episodes/3 days.

The **key end points** derived from subjects' urinary diary data included:

1. Change in average number of toilet voids/day.
2. Change in UUI episodes/day.
3. Volume voided/void.
4. Urge frequency/day.
5. Urge severity.
6. "Dry rate" (no UUI episodes).
7. Stress and total incontinence episodes/day.
8. Total micturitions/day.

D. Statistical Methods:

Categorical data were analysed by PROC FREQ for the Fisher's Exact test, the generalized Cochran-Mantel Haenszel procedure, and the Chi-Square test.

PROC GLM or PROC MIXED was used to run ANOVA models, and homogeneity of variance was assessed using Levene's test, and normality was examined using the Q-Q plots of the residuals and the Shapiro-Wilk statistic.

In studies **IP631-018 and -022**, a total of 1165 subjects were randomized to receive Sanctura XR or the placebo (578 to Sanctura XR and 587 to placebo).

E. Integrated Review of Efficacy Results:

Of the 1165 subjects enrolled at the 129 sites, 1027 completed the study (521 placebo, 88.8% and 506 Sanctura XR, 87.5%). The primary reasons for dropouts were AE's and withdrawal of consent, and the treatment groups were generally similar for the rates and reasons for discontinuation.

Treatment groups were well matched for demographic and baseline characteristics. The majority of subjects were white females, and approximately half of all subjects reported taking other anticholinergics for OAB prior to enrollment. Mean age was 59 for placebo and 60 for Sanctura XR, and ranged from 21-90. Approximately 37% of subjects were \geq than 65 and 9% were \geq than 75.

Baseline characteristics of the treatment groups in the pivotal studies -018 and -022 are seen in Table 1.

Table 1. Population Characteristics

Baseline Characteristic	Placebo N=587	Sanctura XR N=578
Age		
Mean	58.9	60.4
Median (range)	59 (21-90)	61 (21-90)
Categories N (%)		
< 65	365 (65.6%)	352 (60.9%)
65- < 75	144 (24.5%)	141 (24.4%)
≥ 75	58 (9.9%)	85 (14.7%)
Gender N (%)		
Female	505 (86.0%)	484 (83.7%)
Male	82 (14.0%)	94 (16.3%)
Race N (%)		
White	493 (84.1%)	503 (87.0%)
Black	58 (9.9%)	44 (7.6%)
Hispanic	21 (3.6%)	21 (3.6%)
Asian	7 (1.2%)	5 (0.9%)
Other	8 (1.4%)	5 (0.9%)
Height in cm		
Mean	163.8	164.2
Weight in kg		
Mean	86.2	85.2
Prior anticholinergics for OAB, N(%)		
Naive	280 (47.7%)	277 (47.9%)
Non-naïve	307 (52.3%)	301 (52.1%)

Reviewer's Comment: *The baseline characteristics appear to be remarkably well matched between treatment groups.*

1.0 Primary Efficacy Results

The primary objective of this study was to determine the effects of Sanctura XR versus

placebo on the change in the average number of toilet voids/day and the change in the average number of UUI episodes over a 12 week course of treatment in subjects with OAB.

Secondary objectives included assessments of effects on other related symptoms.

1.1 Number of Daily Toilet Voids – Change from Baseline

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in average number of daily toilet voids compared with placebo at week 12. The average reduction of voids/day was from 12.8 at baseline to 10.1 at week 12.

There was also a statistically significant reduction in the average number of UUI episodes/day from 4.1 UUIs/day at baseline to < 1.7 UUIs at Week 12.

The baseline mean values for toilet voids per 24 hours and incontinence episodes per 24 hours were similar between treatment groups.

These results are seen in Table 2.

Table 2. Average (standard error) Changes from Baseline to Weeks 1, 4, and 12.

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value	
Toilet voids		N=576	N=559		
	Baseline	0	12.84 (0.11)	12.81 (0.12)	0.4081
	Change from baseline	1	-1.20 (0.10)	-1.54 (0.11)	0.0020
		4	-1.64 (0.11)	-2.35 (0.11)	<0.0001
		12	-1.90 (0.12)	-2.68 (0.12)	<0.0001
UUI episodes/day		N=576	N=559		
	Baseline	0	4.09 (0.13)	4.07 (0.13)	0.7790
	Change from baseline	1	-1.14 (0.10)	-1.78 (0.10)	<0.0001
		4	-1.63 (0.11)	-2.31 (0.12)	<0.0001
		12	-1.78 (0.12)	-2.42 (0.12)	<0.0001
Volume/toilet void		N=576	N=556		
	Baseline	0	153.97 (2.08)	150.35 (2.07)	0.3285
	Change from baseline	1	12.01 (1.63)	22.79 (1.83)	<0.0001
		4	18.36 (1.97)	29.66 (2.17)	<0.0001
		12	18.36 (2.13)	30.61 (2.31)	<0.0001

In the **secondary efficacy analysis** for average percent change in number of daily toilet voids, Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in average percent change from baseline for number of daily toilet voids compared with placebo at week 12. The average percent reduction was 20 % at week 12. This can be seen in Table 3.

Table 3. Percent Change in Average (SE) Daily Toilet Voids

Rank Analysis of Variance— ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 12.84 (0.11)	N=559 12.81 (0.12)	0.4081
Change from baseline	1	-8.70 (0.74)	-11.41 (0.78)	0.0014
	4	-12.08 (0.84)	-17.82 (0.83)	<0.0001
	12	-14.00 (0.84)	-20.45 (0.86)	<0.0001

1.2 Number of UII Episodes /Day—Change from Baseline

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in the average number of UII episodes/day compared with placebo at week 12. The average reduction from 4 episodes/day at baseline to -1.8/day at week 1 and -2.4 at week 12 with Sanctura. This can be seen in Table 4.

Table 4. Change in Average (SE) UII Episodes/Day

Rank Analysis of Variance— ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 4.09 (0.13)	N=559 4.07 (0.13)	0.7790
Change from baseline	1	-1.14 (0.10)	-1.78 (0.10)	<0.0001
	4	-1.63 (0.11)	-2.31 (0.12)	<0.0001
	12	-1.78 (0.12)	-2.42 (0.12)	<0.0001

Number of UII Episodes /Week—Change from Baseline

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in average number of UII episodes/week compared with placebo at week 12. This can be seen in Table 5.

Table 5. Change in Average (SE) UII Episodes/Week

Rank Analysis of Variance— ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 28.66 (0.92)	N=559 28.47 (0.89)	0.7790
Change from baseline	1	-8.01 (0.70)	-12.49 (0.69)	<0.0001
	4	-11.44 (0.77)	-16.14 (0.82)	<0.0001
	12	-12.46 (0.81)	-16.91 (0.87)	<0.0001

2.0 Secondary Efficacy Results

Secondary efficacy results included complete responder rate, normal void frequency outcome, change in total micturitions/day, change in total urinary incontinence episodes/day, change in stress incontinence episodes/day, dry rate for UUI/day, change in daily urge frequency, change in daily volume voided, normal void frequency outcome, change in OAB symptom score, change in urgency severity, and change in UUI episodes/week.

2.1 Change in Urgency Severity Associated with Toilet Voids

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in average urgency severity associated with toilet voids compared with placebo at week 12.

This can be seen in Table 6.

Table 6. Change in Average (SE) Urgency Severity Associated with Toilet Voids
Rank Analysis of Variance— ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 1.85 (0.02)	N=559 1.85 (0.02)	0.7333
Change from baseline	1	-0.09 (0.02)	-0.18 (0.02)	<0.0001
	4	-0.13 (0.02)	-0.27 (0.02)	<0.0001
	12	-0.15 (0.02)	-0.30 (0.02)	<0.0001

2.2 Daily Volume Voided—Change from Baseline

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) increase in average volume voided / toilet void when compared with placebo at week 12. This can be seen in Table 7.

Table 7. Change in Average (SE) Daily Volume Voided / Toilet Void (mL)
Rank Analysis of Variance— ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 153.97 (2.08)	N=559 150.35 (2.07)	0.3285
Change from baseline	1	12.01 (1.63)	22.79 (1.83)	<0.0001
	4	18.36 (1.97)	29.66 (2.17)	<0.0001
	12	18.36 (2.13)	30.61 (2.31)	<0.0001

2.3 Daily Volume voided-- % Change from Baseline

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) increase in average % change in volume voided / toilet void when compared with placebo at week 12. This can be seen in Table 8.

Table 8. Average (SE) % Change Daily Volume Voided / Toilet Void (mL)

Rank Analysis of Variance— ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 153.97 (2.08)	N=559 150.35 (2.07)	0.3285
Change from baseline	1	9.62 (1.24)	17.53 (1.40)	<0.0001
	4	14.18 (1.53)	22.32 (1.66)	<0.0001
	12	15.04 (21.71)	23.32 (1.79)	<0.0001

2.4 Change in Daily Urge Frequency Associated with Toilet Voids

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in average daily number of urge frequency episodes when compared with placebo at week 12. This can be seen in Table 9.

Table 9. Change in Average (SE) Daily Urge Frequency Associated with Toilet Voids

Rank Analysis of Variance— ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 11.86 (0.12)	N=559 11.76 (0.13)	0.3314
Change from baseline	1	-1.26 (0.12)	-1.69 (0.12)	<0.0007
	4	-1.72 (0.13)	-2.58 (0.13)	<0.0001
	12	-1.99 (0.14)	-2.96 (0.14)	<0.0001

2.5 Stress Incontinence Episodes/Day—Change from Baseline

Sanctura XR failed to demonstrate a statistical or clinically meaningful change in number of stress incontinence episodes/day at week 12. This can be seen in Table 10.

Table 10. Change in Average (SE) Stress Incontinence Episodes/Day

Rank Analysis of Variance—ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 1.32 (0.08)	N=559 1.24 (0.07)	0.7187
Change from baseline	1	-0.52 (0.07)	-0.39 (0.08)	0.25.91
	4	-0.65 (0.08)	-0.57 (0.08)	0.4669
	12	-0.66 (0.07)	-0.73 (0.08)	0.1176

2.6 Total Urinary Incontinence Episodes/Day—Change from Baseline

Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in average number of total urinary incontinence episodes/day when compared with placebo at week 12. This can be seen in Table 11.

Table 11. Change in Average (SE) Total Urinary Incontinence Episodes/Day

Rank Analysis of Variance—ITT : LOCF

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Baseline	0	N=576 4.62 (0.15)	N=559 4.61 (0.14)	0.4288
Change from baseline	1	-1.31 (0.11)	-1.91 (0.10)	<0.0001
	4	-1.84 (0.12)	-2.50 (0.12)	<0.0001
	12	-2.00 (0.13)	-2.68 (0.14)	<0.0001

3.0 Onset of Action

Onset of effect was analyzed to determine the earliest time at which statistically significant efficacy was seen for the selected variables. The time to onset of effect was demonstrated to be superior to placebo as early as day 5 (per diary) during the first week of treatment. This finding was similar to that seen in studies with the 20 mg BID dosage.

4.0 Other Efficacy Endpoints

The findings from the OAB-PGA (Patient Global Assessment) provide supporting evidence that subjects treated with Sanctura XR perceived improvements in toilet void frequency, UUI, and urgency severity as well as overall OAB symptoms. This can be seen in Table 12 where a high positive correlation of OAB-PGA and diary-reported average measures indicates a positive association, while a low negative association indicates an inverse association.

Table 12. Spearman Correlations at Week 12---ITT:LOCF

Question	Placebo N=575 Coefficient (P-Value)	Sanctura XR N=558 Coefficient (P-Value)
Total Voids/Day	0.54 (<0.0001)	0.48 (<0.0001)
UIIs/Day	0.43 (<0.0001)	0.38 (<0.0001)
Urgency Severity/Day	0.37 (<0.0001)	0.47 (<0.0001)
OAB-SCS/Day	0.57 (<0.0001)	0.52 (<0.0001)

5.0 Efficacy Conclusions

The primary efficacy variables for this analysis, based on data from urinary diaries and Week 1, 4 and 12 visits were:

- 1) The change in average number of toilet voids/day.
- 2) The change in UII episodes frequency/day.

Sanctura XR met the 2 primary endpoints at all study visits:

Compared with placebo, there was a statistically significant ($p < 0.0001$) decrease in average number of toilet voids/day from an average of 12.8 at baseline to 10.1 at Week 12.

Compared with placebo, there was a statistically significant ($p < 0.0001$) decrease in average number of UII episodes/day from 4.1 at baseline to < 1.7 at Week 12.

Similar efficacy outcomes were seen across subgroups.

Compared with placebo, the Sanctura XR group also demonstrated statistically significant greater improvements in urgency severity and volume voided/toilet void at Weeks 1, 4 and 12.

Following treatment with Sanctura XR, the number of subjects who had no UIIs steadily improved over 12 weeks: After 1 week there were 15.4 % “dry” subjects; after 4 weeks there were 28.6 % “dry” subjects; and after 12 weeks there were 35.1 % “dry” subjects.

An overall summary of the essential primary and secondary efficacy outcomes derived from diary data can be seen in Table 13.

Table 13. Summary of Results for Selected Diary-Based Efficacy Endpoints---ITT:LOCF

Efficacy Endpoint	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 576	N= 559	
Baseline	0	12.84 (0.11)	12.81 (0.12)	0.4081
Change from Baseline	1	-1.20 (0.10)	-1.54 (0.11)	0.0020
	4	-1.64 (0.11)	-2.35 (0.11)	<0.0001
	12	-1.90 (0.12)	-2.68 (0.12)	<0.0001
UUI Episodes/Day		N=576	N=559	
Baseline	0	4.09 (0.13)	4.07 (0.13)	0.7790
Change from Baseline	1	-1.14 (0.10)	-1.78 (0.10)	<0.0001
	4	-1.63 (0.11)	-2.31 (0.12)	<0.0001
	12	-1.78 (0.12)	-2.42 (0.12)	<0.0001
UUI Episodes/Day-% Change		N=576	N=559	
Baseline	0	3.00	3.33	0.2511
Change from Baseline	1	-33.3	-50.0	<0.0001
	4	-50.0	-71.4	<0.0001
	12	-55.6	-80.0	<0.0001
UUI Episodes/Week		N=576	N=559	
Baseline	0	28.66 (0.92)	28.47 (0.89)	0.7790
Change from Baseline	1	-8.01 (0.70)	-12.49 (0.69)	<0.0001
	4	-11.44 (0.77)	-16.14 (0.82)	<0.0001
	12	-12.46 (0.81)	-16.91 (0.87)	<0.0001
Urgency Severity		N=576	N=559	
Baseline	0	1.85 (0.02)	1.85 (0.02)	0.7333
Change from Baseline	1	-0.09 (0.02)	-0.18 (0.02)	<0.0001
	4	-0.13 (0.02)	-0.27 (0.02)	<0.0001
	12	-0.15 (0.02)	-0.30 (0.02)	<0.0001
Volume/Toilet Void		N=576	N=556	
Baseline	0	153.97 (2.08)	150.35 (2.07)	0.3285
Change from Baseline	1	12.01 (1.63)	22.79 (1.83)	<0.0001
	4	18.36 (1.97)	29.66 (2.17)	<0.0001
	12	18.36 (1.97)	30.61 (2.31)	<0.0001
Urge Frequency		N=576	N=559	
Baseline	0	11.86 (0.12)	11.76 (0.13)	0.3314
Change from Baseline	1	-1.26 (0.12)	-1.69 (0.12)	0.0007

	4	-1.72 (0.13)	-2.58 (0.13)	<0.0001
	12	-1.99 (0.14)	-2.96 (0.14)	<0/0001

Stress Incontinence		N=231	N=244	
Baseline	0	1.32 (0.08)	1.24 (0.07)	0.7187
Change from Baseline	1	-0.52 (0.07)	-0.39 (0.08)	0.2591
	4	-0.65 (0.08)	-0.57 (0.08)	0.4669
	12	-0.66 (0.07)	-0.73 (0.08)	0.1176
Total Incontinence		N=576	N=559	
Baseline	0	4.62 (0.15)	4.61 (0.14)	0.4288
Change from Baseline	1	-1.31 (0.11)	-1.91 (0.10)	<0.0001
	4	-1.84 (0.12)	-2.50 (0.12)	<0.0001
	12	-2.00 (0.13)	-2.68 (0.14)	<0/0001
Normal Void (≤ 8/day)		N=576	N=559	
Baseline	0	1 (0.2 %)		0.3252
Change from Baseline	1	49 (8.5 %)		0.0171
	4	75 (13.0 %)		0
	12	98 (17.0 %)		72 (12.9 %)

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III. Integrated Summary of Safety (ISS)

A. Brief Statement of Conclusions

Both the pivotal studies IP631-018 and IP631-022 were adequate and well-controlled studies conducted in the US. These phase-3 studies provide substantial evidence of safety from data derived from monitoring vital signs, electrocardiograms, physical examinations, clinical laboratory tests and adverse events. Data from the earlier phase-1 and -2 studies provide additional support for the safety of this formulation. The proposed indication, therefore, is well supported by the safety data.

B. Method of Safety Review

The reviewer's basic approach to the safety review involved:

- Review of the proposed indication, protocols, regulatory and scientific background.
- Identification and review of the well-controlled studies to support the indication.
- Conduct of a detailed review of each study involving safety parameters.
- Generate conclusions regarding safety from the pivotal and supporting studies.

C. List of Studies Assessing Safety Variables

The following studies were analyzed in detail during the review process:

- IP631-018 - Pivotal study, Phase-3
- IP631-022 - Pivotal study, Phase-3
- IP631-011 - Supporting Study, Phase-1
- IP631-019 - Supporting Study, Phase-1
- IP631-020 - Supporting Study, Phase-1
- IP631-016 - Supporting Study, Phase-2

D. Safety Results

The protocols of the pivotal studies -018 and -022, being essentially identical, allows for the pooling of the data. The safety assessments were the same for both studies, and the following safety parameters were evaluated and assessed:

1. Vital signs at baseline and at weeks 1, 4, and 12, and in the open-label treatment phase at months 1, 4.5 and 9.
2. AE's recorded from baseline to end of study.
3. ECG's at screening and weeks 1 and 12, and in the open-label treatment phase at months 4.5 and 9.
4. Clinical laboratory tests at screening and week 12, and in the open-label treatment phase at month 9.

5. Physical examinations at baseline and week 12, and in the open-label treatment phase at month 9.

Extent of Exposure:

In the double-blind treatment period, the planned durations of exposure was 84 days. The actual duration of exposure was 80 and 79 days for the placebo and Sanctura XR respectively.

Adverse Events:

AE's are presented by preferred term and MedDRA SOC (system organ class), and all treatment-emergent AEs (TEAEs) are presented irrespective of investigator's assessment of relationship to study drug. The most commonly reported TEAEs were dry mouth, constipation, urinary tract infections, and headache. Dry mouth and constipation were most often reported within the first week of treatment. There was no age-dependent incident rate of AEs between treatment groups. A summary of reported TEAEs of interest is seen in Table 14.

Table 14. Reported TEAE's of Interest

Preferred Term	Number of Subjects (%)	
	Sanctura XR N=578	Placebo N=587
Dry mouth	64 (11.1)	22 (3.7)
Constipation	52 (9.0)	10 (1.7)
Urinary tract infection	42 (7.3)	29 (4.9)
Headache	19 (3.3)	21 (3.6)
Nasopharyngitis	17 (2.9)	10 (1.7)
Nausea	15 (2.6)	16 (2.7)
Upper respiratory infection	13 (2.2)	23 (3.9)
Influenza	13 (2.2)	9 (1.5)
Diarrhea	11 (1.9)	14 (2.4)
Dry eye	10 (1.7)	3 (0.5)
Rash	7 (1.2)	2 (0.3)
Tachycardia	6 (1.0)	3 (0.5)
Urinary retention	5 (0.9)	2 (0.3)
Blurred vision	4 (0.7)	2 (0.3)
Dizziness	3 (0.5)	9 (1.5)
Ischemic stroke	2 (0.3)	0 (0.0)
Myocardial ischemia	1 (0.2)	1 (0.2)
Prolonged QT	1 (0.2)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.2)

Clinical Laboratory Evaluations:

Hematology, serum chemistry, and urinalyses were assessed at screening and week 12. The mean and median changes from baseline to endpoint were generally similar between Sanctura XR and placebo for all laboratory parameters.

Vital Signs and Physical Findings:

There were changes in mean pulse from baseline to endpoint (0.1bpm and 2.8 bpm for placebo and Sanctura XR groups respectively). These changes were consistent with those noted during the trospium 20 mg BID and other anticholinergics in its class. Other observations related to safety were similar between the treatment groups.

ECG Data:

ECGs were assessed at screening and end of study. The PR, QRS and QTcF changes from baseline to endpoint were comparable between treatment groups. There were differences in mean heart rate averages, with the trospium and placebo groups demonstrating a 6.2 bpm and a 1.3 bpm increase respectively.

***Reviewer's Comments:** The safety data derived from this large population provides strong evidence that Sanctura XR is a safe therapy for OAB. The drug was well tolerated, and the reported AEs were generally consistent with those reported with other agents in its class for the same indication. The incidence of AEs in these studies were, for the most part, actually lower than those seen with 20 mg BID dose. There were no SAEs attributed to study drug, and no reported deaths. Subgroup analyses demonstrated consistent outcomes for age, and race.*

Supporting Studies:

Study IP631-011 was conducted to determine the pharmacokinetics (PK) of 4 once-daily oral formulations of Sanctura XR in 25 healthy female subjects. This was a single center, open-label, 5-way crossover pilot study, including a 12-day washout interval between doses. There were 4 delayed release formulations (35, 40, 50 and 60mg capsules) administered once daily (QD), and 20mg tablets given BID. There were 5 treatment periods of 8 days each. A summary of all TEAEs that occurred in at least 2 subjects in the Sanctura XR and the trospium 20 mg BID groups is seen in Table 15. There were no deaths or SAEs.

Table 15.**TEAEs**

Preferred Term	Number of Subjects (%)	
	Sanctura XR N=21	Trospium 20mg BID N=21
Gastrointestinal Disorders		
Constipation	10 (48)	14 (67)
Abdominal distension	7 (33)	8 (38)
Nausea	4 (19)	3 (14)
Flatulence	2 (10)	2 (19)
Dry lips	2 (10)	5 (24)
Loose stools	2 (10)	3 (14)
Dry mouth	2 (10)	2 (10)
Lower abdominal pain	2 (10)	3 (14)
Nervous System Disorders		
Headache	6 (29)	8 (38)
General Disorders		
Feeling hot	3 (14)	0 (0)
Respiratory Disorders		
Nasal congestion	2 (10)	0 (0)
Cardiac Disorders		
Palpitations	2 (10)	3 (14)
Skin Disorders		
Rash papular	2 (10)	0 (0)
Urinary Disorders		
Dysuria	2 (10)	1 (5)
Psychiatric Disorders		
Insomnia	2 (10)	0 (0)

Study IP631-019 characterized the PK and relative bioavailability of Sanctura XR alone or co-administered with antacid in 12 healthy male and female, fasted and fed subjects in an open-label, randomized, 3-period, 3-arm crossover trial.

There were only 2 TEAEs (reported by one subject) in this phase-1 study; herpes simplex and an upper respiratory tract infection. These events were judged by investigator to be unrelated to treatment.

Study IP631-020 was designed to characterize the steady-state PK and relative bioavailability of Sanctura XR 30 and 60 mg QD and trospium 20 mg BID in healthy adult and geriatric subjects and to assess the safety and tolerability of the study drugs. This was a single-center, randomized, open-label, multi-dose, 2-period, 2-arm, crossover study in 24 adults (18-24) and 11 geriatric subjects (65-80). TEAEs reported in at least 2 subjects are seen in Table 16

Table16. TEAEs

Preferred Term	Number of Subjects (%)	
	Sanctura XR N=24	Trospium 20mg BID N=24
Abdominal pain	2 (8.3)	1 (4.2)
Upper abdominal pain	0 (0.0)	2 (8.3)
Back pain	1 (4.2)	2 (8.3)
Hematuria	2 (8.3)	1 (4.2)
Constipation	0 (0.0)	2 (8.3)
Dyspepsia	3 (12.5)	0 (0.0)
Flatulence	2 (8.3)	1 (4.2)
Headache	3 (12.5)	3 (12.5)
Loose stools	1 (4.2)	2 (8.3)
Elevated bilirubin	1 (4.2)	1 (4.2)
Nausea	1 (4.2)	2 (8.3)
Vomiting	1 (4.2)	2 (8.3)

Study IP631-016 evaluated the effects of morning versus evening doses of Sanctura XR on PK, OAB symptoms, and volume voided/toilet void compared with placebo in 148 subjects (ages 18-65) treated for 2 weeks. This was a Phase-2, multicenter, parallel, randomized, double-blind, placebo-controlled trial. Summary safety results of TEAEs in at least 2 subjects in any treatment group are seen in Table17.

Table17.

Preferred Term	TEAEs		
	Number (%)		
	Placebo N=49	Sanctura XR--am N=50	Sanctura XR--pm N=49
Dry mouth	4 (8.2)	6 (12.0)	11 (22.4)
Constipation	0 (0.0)	1 (2.0)	8 (16.3)
Headache	1 (2.0)	3 (6.0)	3 (6.1)
Upper respiratory infection	0 (0.0)	2 (4.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	2 (4.0)	0 (0.0)
Increased blood pressure	0 (0.0)	2 (4.0)	0 (0.0)
Upper abdominal pain	0 (0.0)	2 (4.0)	0 (0.0)
Nausea	0 (0.0)	2 (4.0)	0 (0.0)

Flatulence	0 (0.0)	0 (0.0)	2 (4.1)
Sinus disorder	0 (0.0)	0 (0.0)	2 (4.1)

Reviewer's Comments: *The safety results from these supporting studies provide additional evidence that Sanctura XR is safe and generally well tolerated, with the expected AE's of dry mouth and constipation being common, and associated with other agents of this class.*

IV. Quality of Life (QOL) Assessments:

QOL scales were collected at week 12, and included the King's Health Questionnaire (KHQ) and the OAB-q Health Related Quality of Life (HRQL) score.

The KHQ consists of 21 questions in 9 domains in which higher scores represent a worse QOL and negative changes from baseline are considered an improvement in QOL. As seen in Table 18, the Sanctura XR group demonstrated either significant improvement or a trend toward significant improvement in all domains except General Health perceptions and Personal Relationships changes from baseline at week 12.

Table 18. KHQ Domain at Week 12--- Average (SE) and Rank Analysis of Variance

Domain	Time Point	Week	Placebo N=559	Sanctura XR N=535	p-Value
General Health Perception	Baseline	0	32.04 (0.58)	31.77 (0.60)	0.9084
	Change	12	-3.35 (0.67)	-3.02 (0.67)	0.6244
Incontinence Impact	Baseline	0	81.12 (0.92)	80.06 (1.00)	0.5115
	Change	12	-18.53 (1.30)	-23.52 (1.33)	0.0118
Role Limitations	Baseline	0	63.02 (1.06)	62.23 (1.10)	0.6286
	Change	12	-20.75 (1.33)	-25.89 (1.30)	0.0055
Physical Limitations	Baseline	0	60.23 (1.11)	59.97 (1.14)	0.8227
	Change	12	-19.18 (1.32)	-25.43 (1.42)	0.0007
Social Limitations	Baseline	0	42.16 (1.13)	42.13 (1.21)	0.7346
	Change	12	-13.29 (1.09)	-17.53 (1.18)	0.0155
Personal Relationships	Baseline	0	55.38 (1.53)	57.07 (1.60)	0.4250
	Change	12	-15.42 (1.48)	-16.57 (1.58)	0.4706
Emotions	Baseline	0	46.85 (1.19)	47.36 (1.24)	0.7585
	Change	12	-16.83 (1.17)	-20.95 (1.26)	0.0289
Sleep/Energy	Baseline	0	57.50 (1.11)	56.71 (1.12)	0.6524

Severity	Change	12	-15.80 (1.13)	-20.21(1.19)	0.0218
	Baseline	0	34.07 (0.28)	34.09 (0.31)	0.8707
	Change	12	-9.49 (0.42)	-12.61 (0.43)	<0.0001

The OAB-q HRQL assessment consists of 25 items forming 4 domain subscales. Table 19 presents a summary of the baseline and Week 12 change for the subscales and total scores, demonstrating a statistically significant ($p < 0.02$) improvement (increase) for Sanctura XR over placebo.

Table 19 HRQL Domain at Week 12--- Average (SE) and Rank Analysis of Variance

Domain	Time Point	Week	Placebo N=559	Trospium N=535	p-Value
HRQL Total Score	Baseline	0	51.79 (0.88)	52.11 (0.92)	0.6231
	Change	12	20.73 (0.99)	25.82 (1.03)	0.0003
Concerns/ Worry	Baseline	0	45.85 (0.99)	45.52 (1.07)	0.8528
	Change	12	-18.53 (1.30)	-23.52 (1.33)	0.0118
Coping	Baseline	0	63.02 (1.06)	62.23 (1.10)	0.6286
	Change	12	-20.75 (1.33)	-25.89 (1.30)	0.0055
Social Interactions	Baseline	0	60.23 (1.11)	59.97 (1.14)	0.8227
	Change	12	13.37 (1.32)	-25.43 (0.93)	0.3083
Sleep	Baseline	0	47.93 (1.08)	47.89 (1.11)	0.8868
	Change	12	20.52 (1.14)	24.87 (1.19)	0.0102

QOL assessments are summarized as follows:

Subjects treated with Sanctura XR demonstrated statistically significant or a trend toward significant improvement over placebo in all KHQ domains except General Health Perceptions and Personal Relationships. The Sanctura XR also demonstrated a statistically significant improvement over placebo in all of the OAB-q Symptom Bother items as well as the Symptom Bother/Severity Score.

Reviewer's Comments: *These data demonstrate that the use of Sanctura XR is associated with a modest improvement in QOL, consistent with outcomes from other recent trials with agents of this class.*

V. Appendices: Review of Pivotal Studies IP631-018 and IP631-022 and 120 Day Safety Update

A. Study IP631-018

1.0 Introduction

Overactive bladder syndrome (OAB) is characterized by increased urinary urgency with or without urge urinary incontinence (UUI), usually with frequency and nocturia. OAB is estimated to affect 17 % of adults in the U.S. Hyperactivity of the detrusor muscle can result in bothersome symptoms of OAB that significantly affect overall quality of life.

The goal of pharmacotherapy is to inhibit urge symptoms and involuntary detrusor contractions by relaxing the bladder and increasing bladder capacity, thereby decreasing the number of voids per day. The inhibition of bladder contractility and stabilization of the detrusor muscle has been shown to be effected by agents that block acetylcholine at the muscarinic receptor site.

Anticholinergics are the agents most frequently used to treat OAB, and have demonstrated actions which decrease the number and amplitude of detrusor contractions, increase bladder capacity and improve the symptoms of urgency, frequency and UUI.

Trospium chloride (Sanctura) is a quaternary ammonium derivative of tropine with anticholinergic property that has predominant peripheral antimuscarinic activity which antagonizes the effect of acetylcholine on cholinergically innervated organs and exhibits parasympatholytic action by reducing smooth muscle tone in the urogenital tract. This mechanism enables the detrusor to relax, leading to enhanced bladder compliance with increased capacity and control.

Trospium was first marketed in Germany in 1967 as a spasmolytic agent and received pan-European approval in the 1990's for specific indications including OAB. FDA approval of trospium 20 mg BID for the treatment of OAB occurred in May, 2004. This NDA submission proposes once daily (morning) dose of trospium 60 mg in an extended release capsule (Sanctura XR) for the same indication.

Clinical trials have demonstrated that trospium 20 mg BID reduced OAB symptoms and was generally well tolerated. The most common AE's considered to be at least possibly related to treatment in two 12-week trials were dry mouth (20.1 %), constipation (9.6 %), compared to 8.7% and 9.7% respectively in this submission.

2.0 Study Objectives

The primary objective of this study was to evaluate effects of a single daily AM dosing of Sanctura XR compared with placebo on OAB symptoms with predominant UUI including frequency, urgency severity, and UUI during a 12 week course.

3.0 Investigational Plan

3.1 Efficacy Variables

3.1.1 Primary Efficacy

The co-primary efficacy variables for both studies, based on urinary diary data collected over 3-days prior to baseline, and week 1, 4, and 12 visits were:

1. The change in average number of toilet voids(frequency)/day.
2. The change in UUI episodes /day.

3.1.2 Secondary Efficacy

The secondary efficacy variables were based on urinary diary data for 3 days prior to baseline and each double-blind visit were:

1. UUI episodes frequency/week.
2. Urgency severity with toilet voids.
3. OAB symptom composite score/day.
4. Urge frequency/day.
5. "Dry rate" (no UUI episodes).
6. Stress incontinence episodes frequency/day.
7. Total incontinence episodes frequency/day.
8. Total micturitions/day.
9. Normal void frequency outcome.
10. Complete responder rate outcome.

3.2 Study Design

The study was designed as parallel, randomized, double-blind, placebo-controlled trial of subjects with OAB having predominant UUI.

The 12-week treatment was preceded by a baseline 3-day urinary diary for all subjects. A 7-day washout period was required for subjects currently taking OAB therapies. Subjects were randomized on a 1:1 basis to placebo or Sanctura XR once daily, and were stratified by the average number of voids /day, using the categories 10-15, 15-20, and > 20 average number of voids /day. Subjects were periodically evaluated during the 12-week course, and at study end, offered the option to continue into an open-label phase of the trial, with active drug, for an additional 9 months.

3.3 Dosing Schedule

Subjects were instructed to take a single capsule of study medication in the AM, at least 1 hour before meals, or on an empty stomach (unchewed), with water.

3.4 Study Population

Inclusion Criteria:

1. Male or female subjects \geq age 18.
2. OAB defined as:
 - Urinary frequency of \geq 30 toilet voids/3-days in baseline urinary diary; and;
 - Symptoms of urgency as recorded in baseline diary, ability to differentiate incontinence episodes; and;
 - Pure or mixed urinary incontinence with predominant UUI, and a minimum of 3 UUI episodes/baseline diary.
3. Symptoms of OAB \geq 6 months.
4. Ability to complete baseline diary, on-treatment assessments, and QOL scales.
5. Ability to use bathroom unassisted.
6. Informed consent.
7. Females of childbearing potential must have a negative pregnancy test prior to enrollment, not breastfeeding during study, and use accepted forms of birth control during study.

Exclusion Criteria:

1. Average total urine volume $>$ 3000 mL/day in baseline urinary diary.
2. Total average volume/void $>$ 250 mL in baseline urinary diary.
3. Subjects with predominant stress, insensate, or overflow incontinence.
4. History of neurogenic bladder.
5. Screening serum creatinine $>$ 1.5 mg/dL.
6. Cystic fibrosis in past year or active inflammatory bowel disease.
7. Uninvestigated hematuria.
8. UTI at screening, or recurrent UTI in past year.
9. Post-void residual urine volume $>$ 100 mL.
10. Subjects with indwelling catheter or requiring intermittent catheterization.
11. Bladder surgery within past 6 months, or past surgery with complications.
12. Subjects with interstitial cystitis, bladder cancer within past 6 months, or
current therapy for bladder cancer.
13. PSA $>$ 4 ng/mL.
14. Treatment of OAB within 10 days prior to baseline.
15. Diuretics or estrogens not part of a long-term stable program.
16. Subjects employing bladder retraining/bladder drills program.
17. Subjects who are anticipated to begin or change non-medicinal bladder therapies during the course of study.
18. Prior pelvic malignancy with surgery leading to complications, or requiring radiation therapy.
19. History of myasthenia gravis or closed-angle glaucoma.
20. Hypersensitivity to atropine, oxybutinin, trospium, or excipients in study drug.

21. Any prior exposure to tiroprium, participation in another trial, or receiving a non-approved drug less than 30 days prior to baseline.
22. Working 3rd or swing shift, or regularly waking after noon.

3.4.1 Disposition of Subjects

There were 60 study sites activated in the United States for this study, however subjects were enrolled at only 55 sites.

Tables 1 and 2 summarize the primary screen failure reasons from screening/enrollment logs and Table 3 summarizes reasons for discontinuation from study.

Table 1. Subject Accounting

	Number of Subjects		
	Placebo	Sanctura XR	Total
Screened			1861
Enrolled	303	298	601
Completing N (% enrolled)	273 (90.1)	263 (88.3)	536 (89.2)
Discontinuation N (%)	30 (9.9)	35 (11.7)	65 (10.8)

Table 2. Percent of Screen Failures by Reason

Reason for Failure	Failure Percent
Failed entry criterion for urinary frequency average < 10/day	25 %
Failed entry criterion for UUI < 7/week	7 %
Total daily volume > 3000 mL/day	13 %
Investigator decision or subject schedule	16 %
Unable to correctly complete diary	3 %
Other medical conditions	12 %
Other reasons	24 %

Table 3. Reasons for Discontinuation

Reasons	Number (%) of Subjects	
	Placebo N=303	Sanctura XR N=298
Total	30 (9.9 %)	35 (11.7 %)
Discontinued		
Adverse event	11 (3.6 %)	12 (4.0 %)
Protocol violation	0	2 (0.7 %)
Withdrawn consent	10 (3.3 %)	9 (3.0 %)
Non-compliance	0	3 (1.0 %)

Lost to follow-up	5 (1.7 %)	8 (2.7 %)
Other reason	4 (1.3 %)	1 (0.3 %)

3.5 Treatments

Following enrollment, eligible subjects were randomized to receive either Sanctura XR or matching placebo once daily upon arising, at least 1 hour before meals or on an empty stomach, unchewed with water, for up to 12 weeks of treatment. If a subject was unable to take the dose before noon on any day, the subjects was instructed to omit that day's dose and recommence daily dosing the following morning.

4.0 Integrated Review of Efficacy

4.1 Primary Efficacy Results

Sanctura XR met the 2 primary endpoints at all study visits.

- Sanctura XR demonstrated a statistically significant ($p < 0.0001$) decrease in average number of daily toilet voids (12.8/day at baseline to 10/day at Week 12) compared with placebo.
- Sanctura XR demonstrated a statistically significant ($p=0.0022$) decrease in average number of UUI episodes (> 4 UUIs/day at baseline to < 2 UUIs at Week 12) compared with placebo.

A total of 601 subjects (298 Sanctura XR and 301 placebo) were stratified by average number of baseline voids/day and then randomized 1:1. Subjects were predominantly female (84.8 %), White (86.0 %) and ages 21-90.

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Table 4 demonstrates the baseline characteristics of the treatment groups in this study.

Table 4. Demographic and Baseline Characteristics – Total Patient Sample

Baseline Characteristic	Placebo N=303	Sanctura XR N=298
Age		
Mean	59.3	60.4
Median (range)	59 (27-90)	60 (21-84)
Categories N (%)		
< 65	193 (63.7%)	184 (61.7%)
65- < 75	80 (26.4%)	72 (24.2%)
≥ 75	30 (9.9%)	42 (14.1%)
Gender N (%)		
Female	256 (84.5%)	254 (85.2%)
Male	47 (15.5%)	44 (14.8%)
Race N (%)		
White	259 (85.5%)	258 (86.6%)
Black	30 (9.9%)	26 (8.7%)
Hispanic	7 (2.3%)	9 (3.0%)
Asian	4 (1.3%)	3 (1.0%)
Other	3 (1.0%)	2 (0.7%)
Height in cm		
Mean	163.3	164.8
Weight in kg		
Mean	86.8	85.5
Prior anticholinergics for OAB, N(%)		
Naive	152 (50.2%)	139 (46.6%)
Non-naïve	151 (49.8%)	159 (53.4%)

Sanctura XR demonstrated an average reduction of toilet voids, from 12.8 voids/day at baseline to 10 voids/day at Week 12, compared with placebo ($p < 0.0001$). This is seen in Table 5, where a negative change indicates improvement.

Table 5. Change in Daily Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 300	N= 292	
Baseline	0	12.74 (0.15)	12.78 (0.15)	0.9564
Change from Baseline	1	-1.24 (0.13)	-1.66 (0.14)	0.0092
	4	-1.58 (0.15)	-2.44 (0.15)	<0.0001
	12	-1.99 (0.16)	-2.81 (0.15)	<0.0001

Sanctura XR also demonstrated (secondary analyses) a 22 % average reduction in toilet voids from baseline to Week 12 compared with placebo ($p < 0.0001$), as seen in Table 6.

Table 6. Percent Change in Daily Toilet Voids **ITT:LOCF**

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 300	N= 292	
Baseline	0	12.74 (0.15)	12.78 (0.15)	0.9564
Change from Baseline	1	-9.11 (1.00)	-12.45 (1.05)	0.0106
	4	-11.72 (1.15)	-18.54 (1.10)	<0.0001
	12	-14.80 (1.14)	-21.53 (1.09)	<0.0001

Sanctura XR demonstrated a decrease in the number of diurnal and nocturnal toilet voids ($p=0.0004$), and a trend toward statistical significance ($p= 0.0900$) in decreasing number of nocturnal voids at Week 12, compared with placebo. These results can be seen in Tables 7 and 8.

Table 7. Change in Diurnal Toilet Voids **ITT:LOCF**

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 299	N= 291	
Baseline	0	10.65 (0.14)	10.75 (0.15)	0.7482
Change from Baseline	1	-0.90 (0.12)	-1.34 (0.12)	0.0102
	4	-1.16 (1.13)	-1.84 (0.13)	0.0005
	12	-1.44 (0.14)	-2.12 (0.12)	0.0004

Table 8. Change in Nocturnal Toilet Voids **ITT:LOCF**

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 280	N= 272	
Baseline	0	2.20 (0.08)	2.18 (0.18)	0.9703
Change from Baseline	1	-0.37 (0.07)	-0.37 (0.08)	0.7097
	4	-0.46 (0.06)	-0.66 (0.08)	0.0096
	12	-0.60 (0.07)	-0.75 (0.08)	0.0900

Sanctura XR demonstrated a decrease in average number of UUI episodes/day ($p=0.0022$) and median percent change in number of UUI episodes/day ($p < 0.0001$) compared with placebo at Week 12, as seen in Tables 9 and 10.

Table 9. Change in UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	4.04 (0.20)	4.02 (0.18)	0.5304
Change from Baseline	1	-1.04 (0.15)	-1.70 (0.15)	<0.0001
	4	-1.51 (0.16)	-2.25 (0.16)	<0.0001
	12	-1.62 (0.17)	-2.35 (0.18)	<0.0001

Table 10. Median Percent Change in UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	3.00	3.33	0.1084
Change from Baseline	1	-28.6	-50.0	<0.0001
	4	-46.3	-71.4	0.0003
	12	-52.3	-83.3	<0.0001

Sanctura XR demonstrated a decrease in average percent change in number of diurnal and nocturnal UII episodes/day ($p < 0.0001$ and $p = 0.0504$ respectively) in number of UII compared with placebo at Week 12, as seen in Tables 11 and 12.

Table 11. Average (SE) Percent Change in Diurnal UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	3.43 (0.17)	3.34 (0.15)	0.6765
Change from Baseline	1	-21.2 (3.98)	-41.4 (3.64)	<0.0001
	4	-36.2 (3.90)	-56.8 (3.47)	<0.0001
	12	-35.7 (4.97)	-56.3 (4.53)	<0.0001

Table 12. Average (SE) Percent Change in Nocturnal UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 175	N= 175	
Baseline	0	1.00 (0.06)	1.06 (0.07)	0.6262
Change from Baseline	1	-30.1 (7.87)	-35.7 (7.90)	0.2468
	4	-41.9 (8.20)	-55.7 (6.41)	0.1864
	12	-47.6 (7.64)	-63.1 (6.27)	0.0504

4.2 **Secondary Efficacy Results—Diary Data**

Sanctura XR demonstrated a decrease in average number and median percent change in number of UII episodes/week ($p < 0.0001$) at Week 12 compared with placebo, as seen in Tables 13 and 14.

Table 13. Change in UII Episodes/Week ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	28.98 (1.25)	2815 (1.24)	0.5401
Change from Baseline	1	-7.30 (1.03)	-11.89 (1.04)	<0.0001
	4	-10.58 (1.12)	-15.75 (1.14)	<0.0001
	12	-11.33 (1.20)	-16.43 (1.29)	<0.0001

Table 14. Median Percent Change in UII Episodes/Week ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	21.00	23.33	0.1084
Change from Baseline	1	-28.6	-50.0	<0.0001
	4	-46.3	-71.4	0.0003
	12	-52.3	-83.3	<0.0001

Sanctura XR demonstrated a decrease in average urgency severity associated with daily toilet voids ($p=0.0003$) at Week 12 compared with placebo, as seen in Table 15.

Table 15. Change in Average(SE) Urgency Severity with Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	1.83 (0.03)	1.82 (0.03)	0.8459
Change from Baseline	1	-0.07 (0.02)	-0.16 (0.03)	0.0135
	4	-0.12 (0.03)	-0.28 (0.03)	<0.0001
	12	-0.13 (0.03)	-0.28 (0.03)	0.0003

Sanctura XR demonstrated a decrease in average diurnal and nocturnal urgency severity associated with daily toilet voids at Week 12 ($p=0.0003$ and $p=0.0329$ respectively) compared with placebo, as seen in Tables 16 and 17.

Table 16. Change in Diurnal Urgency Severity with Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	1.79 (0.03)	1.78 (0.03)	0.9477
Change from Baseline	1	-0.07 (0.03)	-0.17 (0.02)	0.0121
	4	-0.11 (0.03)	-0.28 (0.03)	<0.0001
	12	-0.12 (0.03)	-0.28 (0.03)	0.0003

Table 17. Change in Nocturnal Urgency Severity with Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 261	N= 249	
Baseline	0	2.05 (0.04)	2.06 (0.04)	0.8981
Change from Baseline	1	-0.01 (0.04)	-0.11 (0.04)	0.1871
	4	-0.09 (0.04)	-0.22 (0.05)	0.0259
	12	-0.06 (0.05)	-0.23 (0.05)	0.0329

Sanctura XR demonstrated a decrease in average and average percent change in OAB-SCS at Week 12 compared with placebo, as seen in Tables 18 and 19.

Table 18. Change in Daily OAB-SCS ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	37.09 (0.66)	36.75 (0.67)	0.6232
Change from Baseline	1	-4.09 (0.64)	-6.03 (0.60)	0.0017
	4	-6.33 (0.71)	-9.31 (0.68)	0.0002
	12	-6.49 (0.73)	-9.84 (0.75)	0.0002

Table 19. Percent Change in Daily OAB-SCS ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	37.09 (0.66)	36.75 (0.67)	0.6232
Change from Baseline	1	-9.23 (1.45)	-15.27 (1.47)	0.0009
	4	-15.10 (1.64)	-24.48 (1.61)	<0.0001
	12	-15.53 (1.74)	-26.14 (1.78)	<0.0001

Sanctura XR demonstrated an increase in average volume and average percent change in volume voided/toilet void at Week 12 ($p=0.0039$ and $p=0.0041$ respectively) compared with placebo, as seen in Tables 20 and 21.

Table 20. Change in Daily Volume Voided/Toilet Void ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 300	N= 290	
Baseline	0	155.93 (3.01)	151.03 (2.91)	0.3005
Change from Baseline	1	12.07 (2.11)	21.61 (2.76)	0.0036
	4	17.24 (2.47)	30.00 (3.14)	0.0007
	12	18.89 (2.79)	29.77 (3.16)	0.0039

Table 21. Percent Change in Daily Volume Voided/Toilet Void ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 300	N= 290	
Baseline	0	155.93 (3.01)	151.03 (2.91)	0.3005
Change from Baseline	1	9.55 (1.55)	16.09 (1.97)	0.0041
	4	13.47 (1.92)	21.56 (2.23)	0.0008
	12	15.55 (2.34)	21.99 (2.38)	0.0041

Trospium demonstrated a decrease in average daily number of urge frequency episodes at Week 12 compared with placebo ($p < 0.0001$), as seen in Table 22.

Table 22. Change in Daily Urge Frequency Associated with Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 300	N= 292	
Baseline	0	11.80 (0.17)	11.86 (0.17)	0.8803
Change from Baseline	1	-1.34 (0.16)	-1.90 (0.16)	0.0033
	4	-1.71 (0.18)	-2.66 (0.17)	0.0003
	12	-2.12 (0.19)	-3.11 (0.17)	<0.0001

Trospium was superior to placebo ($p = 0.0055$) with respect to percent of subjects completely dry at Week 12, as seen in Table 23.

Table 23. Number (5) of Subjects Dry for UII—ITT:LOCF

	Week	Placebo N=300	Trospium N=292	P-Value ^a
Baseline	0	0	0	Not applicable
On-Treatment	1	23 (7.7%)	43 (14.7%)	0.0065
	4	51 (17.0%)	82 (28.1%)	0.0014
	12	72 (24.0%)	101 (34.6%)	0.0055

^a P-value from a CMH test, controlling for pooled center.
ITT = intent-to-treat, LOCF = last observation carried forward data set.

Sanctura XR failed to demonstrate either a statistical or numerical decrease in the average number of stress incontinence episodes at any week compared with placebo, as seen in Table 24.

Table 24. Change in Average (SE) Stress Incontinence Episodes ITT:LOCF

	Week	Placebo N= 122	Sanctura XR N= 113	P-Value
Baseline	0	1.28 (0.11)	1.11 (0.09)	0.3168
Change from Baseline	1	-0.62 (0.09)	-0.44 (0.08)	0.0933
	4	-0.67 (0.12)	-0.52 (0.10)	0.1103
	12	-0.75 (0.10)	-0.61 (0.10)	0.6506

Sanctura XR demonstrated a decrease in average number of total urinary incontinence episodes per day at Week 12 compared with placebo ($p = 0.0043$), as seen in Table 25.

Table 25. Change in Average (SE) Total Urinary Incontinence Episodes/Day ITT:LOCF

	Week	Placebo N= 300	Sanctura XR N= 292	P-Value
Baseline	0	4.66 (0.21)	4.54 (0.19)	0.8915
Change from Baseline	1	-1.46 (0.15)	-1.98 (0.13)	0.0025
	4	-1.97 (0.17)	-2.47 (0.17)	0.0133
	12	-2.20 (0.17)	-2.62 (0.17)	0.0043

Sanctura XR demonstrated a decrease in average number of total micturitions per day at Week 12 compared with placebo ($p < 0.0001$), as seen in Table 26.

Table 26. Change in Total Micturitions/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 300	N= 292	
Baseline	0	12.96 (0.16)	12.89 (0.15)	0.8329
Change from Baseline	1	-1.28 (0.14)	-1.69 (0.15)	0.0159
	4	-1.64 (0.16)	-2.53 (0.15)	<0.0001
	12	-2.10 (0.16)	-2.90 (0.15)	<0.0001

Sanctura XR was superior to placebo (p=0.0022) in the percent of subjects with a normal void frequency (\leq voids/day) at week 12, as seen in Table 27.

Table 27. Number (%) of Subjects with \leq 8 Voids/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 300	N= 292	
Baseline	0	1 (0.3)	0	0.3252
On-Treatment	1	27 (9.0)	41 (14.0)	0.0660
	4	38 (12.7)	68 (23.3)	0.0008
	12	54 (18.0)	84 (28.8)	0.0022

Sanctura XR was superior to placebo (p=0.0027) in percent of subjects completely responding (no UUI episodes and \leq 8 voids/day) at week 12, as seen in Table 28.

Table 28. Number (%) of Complete Responders ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 300	N= 292	
Baseline	0	0	0	N/A
On-Treatment	1	12 (4.0)	24 (8.2)	0.0428
	4	16 (5.3)	51 (17.5)	<0.0001
	12	34 (11.3)	60 (20.5)	0.0027

4.3 Other Efficacy Endpoints

In the Kings Health Questionnaire, the Sanctura XR group improvement over placebo (p=0.0023) only in the Severity Measures domain, as seen in Table 29.

Table 29. KHQ Domain at Baseline and Week 12—Average (SE) ITT:LOCF

Domain	Time Point	Week	Placebo N=292	Sanctura XR N=278	p-Value
General Health Perception	Baseline	0	24.74 (1.03)	24.37 (0.99)	0.7673
	Change	12	-3.72 (0.98)	-3.02 (0.89)	0.0785
Incontinence Impact	Baseline	0	81.62 (1.35)	80.82 (1.43)	0.6210
	Change	12	-20.92 (1.78)	-23.67 (1.83)	0.3144
Role Limitations	Baseline	0	61.69 (1.62)	60.99 (1.63)	0.5424
	Change	12	-26.05 (1.85)	-25.75 (1.74)	0.8123
Physical Limitations	Baseline	0	57.53 (1.69)	57.10 (1.69)	0.8032
	Change	12	20.44 (1.80)	-24.29 (1.93)	0.3266
Social Limitations	Baseline	0	12.07 (0.35)	-11.79 (0.37)	0.4168
	Change	12	-3.98 (0.33)	-4.23 (0.33)	0.9594
Personal Relationships	Baseline	0	38.64 (2.16)	40.31 (2.20)	0.4897
	Change	12	-19.20 (2.11)	-15.03 (2.24)	0.2581
Emotions	Baseline	0	45.85 (1.73)	45.04 (1.70)	0.8715
	Change	12	-17.60 (1.63)	-20.90 (1.63)	0.2144
Sleep/Energy	Baseline	0	56.91 (1.56)	55.96 (1.56)	0.4322
	Change	12	-16.96 (1.56)	-19.44 (1.60)	0.4123
Severity	Baseline	0	34.19 (0.39)	34.76 (0.44)	0.3232
	Change	12	-10.45 (0.56)	-12.98 (0.58)	0.0023

As seen in Table 30, the Sanctura XR group failed to demonstrate a statistically significant improvement over placebo in the OABq QOL questionnaire.

Table 30. HRQL Domain at Week 12--- Average (SE) ITT:LOCF

Domain	Time Point	Week	Placebo N=292	Sanctura XR N=278	p-Value
HRQL Total Score	Baseline	0	49.86 (1.24)	50.33 (1.27)	0.6255
	Change	12	23.53 (1.33)	27.42 (1.39)	0.1232
Concerns/Worry	Baseline	0	44.10 (1.40)	43.38 (1.44)	0.7716
	Change	12	-26.83 (1.56)	-35.06 (1.66)	0.0054
Coping	Baseline	0	46.07 (1.44)	47.79 (1.46)	0.3336
	Change	12	-24.25 (1.51)	-28.36 (1.57)	0.1792
Social Interactions	Baseline	0	71.73 (1.39)	73.36 (1.43)	0.3318
	Change	12	15.92 (1.31)	-16.90 (1.33)	0.9535
Sleep	Baseline	0	45.87 (1.48)	45.70 (1.54)	0.9595
	Change	12	23.76 (1.52)	26.90 (1.58)	0.2844

The Sanctura XR group demonstrated an improvement over placebo ($p < 0.05$) in most of the Symptom Bother and Symptom Bother/Severity scales, as seen in Table 31.

Table 31. OABq QOL Questionnaire at Baseline and Change to Week 12; ITT:LOCF

		Placebo	Trospium	
Domain	Time Point ^a	N=292 ^c	N=278 ^c	P-Value ^b
Total Symptom Bother/Severity Score	Baseline	65.47 (0.97)	66.89 (1.09)	0.3232
	Change from Baseline	-26.14 (1.40)	-32.45 (1.45)	0.0023
Frequent Urination During the Daytime Hours	Baseline	4.52 (0.06)	4.71 (0.06)	0.0480
	Change from Baseline	-1.30 (0.08)	-1.73 (0.09)	0.0003
An Uncomfortable Urge to Urinate	Baseline	4.29 (0.06)	4.38 (0.07)	0.2151
	Change from Baseline	-1.37 (0.08)	-1.59 (0.09)	0.0545
A Sudden Urge to Urinate with Little or No Warning	Baseline	4.26 (0.07)	4.35 (0.07)	0.2962
	Change from Baseline	-1.34 (0.10)	-1.72 (0.10)	0.0123
Accidental Loss of Small Amounts of Urine	Baseline	4.11 (0.07)	4.24 (0.08)	0.2331
	Change from Baseline	-1.27 (0.09)	-1.67 (0.09)	0.0025
Night Time Urination	Baseline	4.27 (0.08)	4.18 (0.08)	0.4114
	Change from Baseline	-1.18 (0.09)	-1.31 (0.09)	0.1641
Waking up at Night Because you had to Urinate	Baseline	4.29 (0.08)	4.34 (0.08)	0.8181
	Change from Baseline	-1.22 (0.09)	-1.44 (0.09)	0.1053
An Uncontrollable Urge to Urinate	Baseline	4.28 (0.07)	4.30 (0.08)	0.7726
	Change from Baseline	-1.44 (0.10)	-1.77 (0.09)	0.0216
Urine Loss Associated with a Strong Desire to Urinate	Baseline	4.16 (0.07)	4.26 (0.08)	0.3575
	Change from Baseline	-1.32 (0.10)	-1.75 (0.10)	0.0035

^a Higher baseline scores indicate worse quality of life. A negative change (decrease from baseline) indicates improvement.
^b Rank ANOVA Model
^c Number of patients contributing differs from domain to domain, and is generally less than the overall N presented here.

Sanctura XR demonstrated a statistically significant decrease in average number of daily toilet voids at Week 12 when compared with placebo. Subjects experienced an average reduction from 12.8 voids per day at baseline to less than 10 toilet voids per day at Week 12.

Sanctura XR demonstrated decrease in average number of UUI episodes per day at Week 12 when compared with placebo. Subjects treated with trospium experienced an

average reduction from over 4 UUIs per day at baseline to less than 2 UUIs per day at Week 12.

The Sanctura XR group demonstrated statistically significantly greater improvements in toilet voids, UUIs, urgency severity associated with toilet voids, and volume voided per toilet void, compared to placebo at Week 12 as well as at Weeks 4 and 1.

The time to onset of effect across study days was demonstrated to be superior for the Sanctura XR group compared with the placebo group as early as Day 5.

Findings for changes in diurnal and nocturnal outcomes were consistent with the overall symptom findings, demonstrating that the Sanctura XR formulation provides effective symptomatic relief following a single morning dose.

Following treatment with Sanctura XR, the number of subjects who had no UUI episodes steadily improved over 12 weeks of treatment. After 1 week of treatment there were 43 (14.7% “dry” subjects (no UUI), After 4 weeks there were 82 (28.1%) “dry” subjects and after 12 weeks of treatment there were 101 (34.6% “dry” subjects.

A Complete Responder was defined as having no UUIs and a void frequency of ≤ 8 voids/day. Sanctura XR was statistically significantly superior to placebo in the percent of subjects completely responding at week 12.

5.0 Integrated Review of Safety

Brief Statement of Conclusions:

The adverse events associated with this formulation of trospium appears to be similar to that seen with other anticholinergics used to treat OAB. Dry mouth and constipation were the AE's reported with the highest incidence (approximately 9%) which was lower than that seen with 20 mg BID regimen. Excepting urinary tract infections reported in 7 % of subjects, other AE's were seldom reported. When the investigator judged the relationship of UTI to study drug, the incidence decreased to 1.2 %. There were no deaths in any treatment group.

5.1 Extent of Exposure

The average duration of exposure to the double-blind medication is summarized in Table 32.

Table 32. Duration of Exposure (Days)

	Placebo N = 303	Trospium N = 298
Number of patients with exposure information ^a	N = 296	N = 288
Mean (SE)	80.4 (0.95)	79.2 (1.04)
Median	84	84
Range (minimum to maximum)	2 - 109	3 - 100

5.2 Adverse Events

Treatment-emergent AE's (TEAEs) reported in 2% or more subjects in either treatment group is presented in Table 33 by preferred term in decreasing order of frequency based on trospium incidence.

Table 33. TEAEs Reported in at Least 2% of Subjects in Either Group

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 303	Trospium N = 298
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Constipation	5 (1.7)	29 (9.7)
Dry mouth	9 (3.0)	26 (8.7)
Urinary tract infection	12 (4.0)	18 (6.0)
Upper respiratory tract infection	16 (5.3)	8 (2.7)
Dyspepsia	3 (1.0)	8 (2.7)
Sinusitis	6 (2.0)	7 (2.3)
Nasopharyngitis	6 (2.0)	5 (1.7)
Headache	12 (4.0)	4 (1.3)
Diarrhoea	6 (2.0)	4 (1.3)
Back pain	9 (3.0)	3 (1.0)
Nausea	6 (2.0)	3 (1.0)

A higher incidence of constipation, UTI, and dyspepsia was seen in the Sanctura XR subgroup of subjects ≥ 65 years old compared with younger subjects. Table 34 presents the incidence of the most frequently reported TEAs by these ages.

Table 34. Incidence of Most Commonly Reported TEAEs by Age Subgroups

MedDRA Preferred term	Number of patients (%)			
	Placebo N = 303		Trospium N = 298	
	< 65 years (N=193)	≥ 65 years (N=110)	< 65 years (N=184)	≥ 65 years (N=114)
Total patients with at least 1 TEAE	96 (49.7)	51 (46.4)	111 (60.3)	59 (51.8)
Constipation	2 (1.0)	3 (2.7)	13 (7.1)	16 (14.0)
Dry Mouth	8 (4.1)	1 (0.9)	16 (8.7)	10 (8.8)
Urinary tract infection	7 (3.6)	5 (4.5)	6 (3.3)	12 (10.5)
Upper respiratory tract infection	10 (5.2)	6 (5.5)	6 (3.3)	2 (1.8)
Dyspepsia	3 (1.6)	0 (0.0)	2 (1.1)	6 (5.3)

The relative proportion of the incidence of TEAEs by severity were comparable between groups, and is summarized in Table 35.

Table 35. Incidence of TEAEs by Severity

TEAE severity	Number of patients (%)	
	Placebo N = 303	Trospium N = 298
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Mild	77 (25.4)	81 (27.2)
Moderate	61 (20.1)	75 (25.2)
Severe	9 (3.0)	14 (4.7)

TEAEs of interest included expected anticholinergic events. Other AEs of interest include nervous system disorders and cardiac-related events. These events of interest are presented in Table 36.

Table 36. TEAEs of Interest by Preferred Term

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 303	Trospium N = 298
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Constipation	5 (1.7)	29 (9.7)
Dry mouth	9 (3.0)	26 (8.7)
Urinary tract infection	12 (4.0)	18 (6.0)
Tachycardia	1 (0.3)	4 (1.3)
Headache	12 (4.0)	4 (1.3)
Dry eye	2 (0.7)	4 (1.3)
Urinary retention	1 (0.3)	4 (1.3)
Rash	0 (0.0)	4 (1.3)
Blurred vision	2 (0.7)	3 (1.0)
Myocardial ischemia	0 (0.0)	1 (0.3)
Dizziness	5 (1.7)	1 (0.3)
Age-indeterminate myocardial infarction	1 (0.3)	0 (0.0)

TEAEs judged by investigator to be at least possibly related to study treatment in at least 1% of subjects in either group are seen in Table 37 in decreasing frequency based on rates in the trospium group.

Table 37. Incidence of Possibly Related TEAEs in at Least 1% of Subjects

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 303	Sanctura XR N = 298
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Total patients with at least 1 TEAE at least possibly related	53 (17.5)	78 (26.2)
Constipation	4 (1.3)	28 (9.4)
Dry mouth	9 (3.0)	26 (8.7)
Dyspepsia	3 (1.0)	6 (2.0)
Urinary tract infection	3 (1.0)	6 (2.0)

Dry eye	1 (0.3)	4 (1.3)
Urinary retention	1 (0.3)	4 (1.3)
Vision blurred	2 (0.7)	3 (1.0)
Abdominal distension	1 (0.3)	3 (1.0)
Abdominal pain	2 (0.7)	3 (1.0)
Abdominal pain lower	3 (1.0)	3 (1.0)
Constipation aggravated	3 (1.0)	3 (1.0)
Nausea	2 (0.7)	3 (1.0)
Headache	8 (2.6)	3 (1.0)
Dry skin	0 (0.0)	3 (1.0)
Abdominal discomfort	3 (1.0)	1 (0.3)
Diarrhoea	3 (1.0)	1 (0.3)
Dizziness	4 (1.3)	1 (0.3)
Abdominal pain upper	3 (1.0)	0 (0.0)

5.3 Deaths, Other SAE's, and Other Significant AE's

No subject died during this study. The incidence of all treatment-emergent SAEs is seen in Table 38. There were no SAE's judged to be at least possibly related to study drug.

Table: 38 Treatment Emergent SAE's

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 303	Trospium N = 198
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Total patients with at least 1 Treatment-emergent SAE	5 (1.7)	3 (1.0)
Angina pectoris	1 (0.3)	0 (0.0)
Coronary artery disease	1 (0.3)	0 (0.0)
Duodenal ulcer haemorrhage	0 (0.0)	1 (0.3)
Colitis	1 (0.3)	0 (0.0)
Noncardiac chest pain	1 (0.3)	0 (0.0)
Biliary dyskinesia	0 (0.0)	1 (0.3)
Tracheobronchitis	1 (0.3)	0 (0.0)
B-cell lymphoma	0 (0.0)	1 (0.3)
Dizziness	1 (0.3)	0 (0.0)

As seen in the above Table 38, few subjects experienced an “other significant” AE, and the treatments groups were comparable in these instances. No subjects required a dose reduction.

The incidence of **Other Significant TEAE’s** is seen in Table 39.

Table 39.

Other significant TEAE criterion	Placebo N = 303	Trospium N = 298
Led to discontinuation of study medication	11 (3.6)	12 (4.0)
Led to temporary interruption of study medication	8 (2.6)	8 (2.7)
Required dose reduction of study medication	0	0

The incidence of AE’s leading to discontinuation of study drug is seen in Table 40.
Table 40. TEAE’s Leading to Study Drug Discontinuation

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 303	Trospium N = 298
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Total patients with at least 1 TEAE Leading to Discontinuation of Study Medication	11 (3.6)	12 (4.0)
Constipation	0 (0.0)	3 (1.0)
Urinary retention	0 (0.0)	2 (0.7)
Dry mouth	0 (0.0)	2 (0.7)
Rash	0 (0.0)	1 (0.3)
Nasal dryness	0 (0.0)	1 (0.3)
Flatulence	0 (0.0)	1 (0.3)
Faecaloma	0 (0.0)	1 (0.3)
Dyspepsia	1 (0.3)	1 (0.3)
Chest wall pain	0 (0.0)	1 (0.3)
Biliary dyskinesia	0 (0.0)	1 (0.3)
Abdominal pain	0 (0.0)	1 (0.3)
Abdominal discomfort	1 (0.3)	1 (0.3)
Coronary artery disease	1 (0.3)	0 (0.0)
Visual disturbance	1 (0.3)	0 (0.0)
Vision blurred	2 (0.7)	0 (0.0)
Urinary tract infection	1 (0.3)	0 (0.0)
Micturition urgency	1 (0.3)	0 (0.0)
Headache	2 (0.7)	0 (0.0)
Dizziness	4 (1.3)	0 (0.0)
Constipation aggravated	1 (0.3)	0 (0.0)

AE's leading to temporary interruption of study drug are seen in Table 41.

Table 41. Incidence of TEAE's Leading to Study Drug Interruption

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 303	Trospium N = 298
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Total patients with at least 1 TEAE where the study medication was temporarily interrupted	8 (2.6)	8 (2.7)
Constipation	0 (0.0)	3 (1.0)
Anaemia	0 (0.0)	1 (0.3)
Abdominal pain	0 (0.0)	1 (0.3)
Abdominal pain lower	0 (0.0)	1 (0.3)
Dry mouth	0 (0.0)	1 (0.3)
Duodenal ulcer haemorrhage	0 (0.0)	1 (0.3)
Gastric ulcer	0 (0.0)	1 (0.3)
Hiatus hernia	0 (0.0)	1 (0.3)
Stomach discomfort	0 (0.0)	1 (0.3)
Labyrinthitis	0 (0.0)	1 (0.3)
Urinary retention	0 (0.0)	1 (0.3)
Influenza	1 (0.3)	1 (0.3)
Abdominal pain upper	1 (0.3)	0 (0.0)
Colitis	1 (0.3)	0 (0.0)
Dyspepsia	1 (0.3)	0 (0.0)
Gastroenteritis	1 (0.3)	0 (0.0)
Gastroenteritis viral	1 (0.3)	0 (0.0)
Upper respiratory tract infection	1 (0.3)	0 (0.0)
Urine abnormality	1 (0.3)	0 (0.0)
Vaginal haemorrhage (female patients only)	1 (0.4)	0 (0.0)

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5.4 Clinical Laboratory Evaluations

Potentially Clinically Significant (PCS) Hematology Values are seen in Table 42

Table 42. Abnormal Values Reported in at least 2 Subjects at Endpoint

Hematology PCS abnormal value	Placebo N = 303		Trospium N = 298	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Hematology PCS abnormal value	3/274 (1.1)	2/272 (0.7)	5/272 (1.8)	3/270 (1.1)
Eosinophils High ($\geq 10\%$)	3/274 (1.1)	2/271 (0.7)	0/272 (0.0)	0/269 (0.0)
Hematocrit Low (F: $\leq 32\%$ M: $\leq 37\%$)	0/274 (0.0)	0/272 (0.0)	2/272 (0.7)	0/268 (0.0)
Hemoglobin Low (F: ≤ 9.5 g/dL M: ≤ 11.5 g/dL)	0/274 (0.0)	0/272 (0.0)	2/272 (0.7)	2/269 (0.7)

n = total patients who met PCS criteria at endpoint after baseline.
N = total patients who had laboratory values for the analyte at any point after baseline (including patients who had a missing value at baseline).
N at BL = normal at baseline, the number of patients who met PCS criteria for the analyte at endpoint after Baseline and whose Baseline value was normal.
PCS = potentially clinically significant. F=female, M=male

5.4.2 Serum chemistry PCS abnormal values at endpoint are summarized for all parameters reported in at least 2 subjects in either treatment group are seen in Table 43.

Table 43. PCS Abnormal Serum Chemistry Values

Chemistry PCS abnormal value	Placebo N = 303		Trospium N = 298	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Chemistry PCS abnormal value	26/287 (9.1)	22/287 (7.7)	33/275 (12.0)	23/275 (8.4)
Urea Nitrogen (BUN) High (≥ 30 mg/dL)	4/286 (1.4)	4/285 (1.4)	11/275 (4.0)	5/265 (1.9)
Uric Acid High (F ≥ 8.5 M: ≥ 10.5 mg/dL)	4/286 (1.4)	2/280 (0.7)	1/275 (0.4)	1/274 (0.4)
Bilirubin – Direct High (≥ 0.5 mg/dL)	5/286 (1.7)	5/285 (1.8)	3/275 (1.1)	3/273 (1.1)
Glucose High (> 250 mg/dL)	4/286 (1.4)	2/284 (0.7)	2/275 (0.7)	1/271 (0.4)
HDL Low (≤ 30 mg/dL)	3/286 (1.0)	2/282 (0.7)	8/275 (2.9)	7/273 (2.6)
LDL High (≥ 200 mg/dL)	2/286 (0.7)	1/280 (0.4)	2/275 (0.7)	1/273 (0.4)
Calcium Low (< 8.2 mg/dL)	4/286 (1.4)	4/284 (1.4)	3/275 (1.1)	3/273 (1.1)
Potassium High (≥ 6 mmol/L)	1/285 (0.4)	1/285 (0.4)	4/275 (1.5)	4/275 (1.5)

n = total patients who met PCS criteria at any point after Baseline.
N = total patients who had laboratory values for the analyte at Endpoint after Baseline (including patients who had a missing value at Baseline).
N at BL = normal at Baseline, the number of patients who met PCS criteria for the analyte at Endpoint after Baseline and whose Baseline value was normal.
PCS = potentially clinically significant. F=female, M=male

5.4.3 Urinalysis PCS abnormal values at endpoint are summarized for all parameters reported in at least 2 subjects in either treatment group are seen in Table 44.

Table 44. Urinalysis: PCS Abnormal Values Reported in at least 2 Subjects at Endpoint

Urinalysis PCS abnormal value	Placebo N = 303		Trospium N = 298	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Urinalysis PCS abnormal value	82/287 (26.8)	73/287 (25.4)	80/276 (29.0)	68/276 (24.6)
Blood High (≥ 3+)	5/287 (1.7)	5/286 (1.7)	1/276 (0.4)	1/272 (0.4)
Protein High (≥ 2+)	1/287 (0.3)	1/287 (0.3)	3/276 (1.1)	1/274 (0.4)
RBC/HPF High [(11-20)(21-40)(TNTC) /HPF]	9/287 (3.1)	6/282 (2.1)	7/276 (2.5)	6/270 (2.2)
WBC/HPF High [(11-20)(21-40)(TNTC) /HPF]	16/287 (5.6)	12/279 (4.3)	22/276 (8.0)	18/269 (6.7)
Hyaline Casts / LPF High [(3-20)(>20)(TNTC) /LPF]	4/287 (1.4)	4/285 (1.4)	3/276 (1.1)	3/274 (1.1)
Epithelial Cells / HPF High [(>20)(TNTC)]	9/287 (3.1)	7/274 (2.6)	7/276 (2.5)	7/267 (2.6)
Squamous Epith Cells / HPF High [(>20)(TNTC)]	16/287 (5.6)	13/271 (4.8)	12/276 (4.3)	10/255 (3.9)
Round Epith Cells / HPF High [(>20)(TNTC)]	2/287 (0.7)	2/287 (0.7)	0/276 (0.0)	0/276 (0.0)
Bacteria / HPF High [(21-40)(TNTC)]	16/287 (5.6)	13/271 (4.8)	12/276 (4.3)	10/255 (3.9)
Amorphous Sediment / HPF High (TNTC)	28/287 (9.8)	23/262 (8.8)	28/276 (10.1)	23/262 (8.8)
Calcium Oxalate Crystals / HPF High [(>20)(TNTC)]	22/287 (7.7)	19/273 (7.0)	14/276 (5.1)	14/269 (5.2)
Triple Phosph Crystals / HPF High [(>20)(TNTC)]	0/287 (0.0)	0/287 (0.0)	2/276 (0.7)	2/276 (0.7)
Uric Acid Crystals / HPF High [(>20)(TNTC)]	5/287 (1.7)	5/284 (1.8)	0/276 (0.0)	0/272 (0.0)

n = total patients who met PCS criteria at any point after Baseline.
N = total patients who had laboratory values for the analyte at Endpoint after Baseline (including patients who had a missing value at Baseline).
N at BL = normal at Baseline, the number of patients who met PCS criteria for the analyte at Endpoint after Baseline and whose Baseline value was normal.
Epith = epithelial, HPF = high-powered field, PCS = potentially clinically significant,
RBC = red blood cells. WBC = white blood cells.

5.4.4 Vital Signs, Physical Findings and Other Observations Related to Safety

5.4.5 Pulse

Descriptive statistics for pulse recorded at baseline and endpoint are summarized in Table 45.

Table 45.

Pulse at Baseline and Endpoint

		Placebo N = 303	Trospium N = 298
Baseline	Mean (SE)	71.7 (0.57)	71.7 (0.58)
	Median	72	71.5
	Range	48 - 103	52 - 100
Endpoint	Mean (SE)	71.5 (0.55)	74.0 (0.59)
	Median	72	73
	Range	45 - 102	51 - 102
Change	Mean (SE)	-0.2 (0.54)	2.3 (0.54)
	Median	0	2
	Range	-28 to 26	-20 to 35

SE=Standard Error

5.4.6 **Blood Pressure.** The vital signs PCS abnormal values (noted at any time) in at least 2 subjects are summarized Table 46. Vital Signs: High or Low PCS Abnormal Values

Vital Sign Parameter	Placebo N = 303		Trospium N = 298	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Systolic blood pressure:				
Low: < 90 or decrease \geq 20 mm Hg	53/298 (17.8)	51/296 (17.2)	38/287 (13.2)	38/283 (13.4)
High: >180 or increase \geq 20 mm Hg	18/298 (6.0)	18/296 (6.1)	20/287 (7.0)	19/283 (6.7)
Diastolic blood pressure:				
Low: < 50 or decrease \geq 15 mm Hg	29/298 (9.7)	29/298 (9.7)	17/287 (5.9)	17/286 (5.9)
High: >105 or increase \geq 15 mm Hg	13/298 (4.4)	13/298 (4.4)	22/287 (7.7)	22/286 (7.7)
Pulse				
Low: Decrease \geq 15 bpm	27/298 (9.1)	27/296 (9.1)	10/287 (3.5)	10/286 (3.5)
Low: <50, Decrease \geq 15 bpm or both	28/298 (9.4)	28/296 (9.4)	10/287 (3.5)	10/286 (3.5)
High: >100 and Increase \geq 15 bpm	2/298 (0.7)	2/296 (0.7)	1/287 (0.3)	1/286 (0.3)
High: >100 and Increase \geq 15 bpm or >120 and Increase <15 bpm	2/298 (0.7)	2/296 (0.7)	1/287 (0.3)	1/286 (0.3)

n = total patients who met PCS criteria at any point post baseline.
N = total patients who had a vital sign measurement recorded after baseline (including patients who had a missing value at baseline)
N at BL = normal at baseline, the number of patients who met PCS criteria for the vital signs at any time point after baseline, and whose baseline vital signs were normal
PCS = potentially clinically significant.

5.4.7 Descriptive ECG parameters summarized in Tables 47 and 48.

Table 47. Heart Rate and Changes in QT and QTcF Intervals

ECG Parameter	Placebo N = 303	Trospium N = 298
PR interval (msec) N	285	259
Mean (SE)	0.3 (1.14)	-2.1 (1.31)
Median	0.0	-2.0
Range	-150.0 to 120.0	-113.0 to 192.0
QRS interval (msec) N	287	272
Mean (SE)	0.2 (0.58)	0.4 (0.58)
Median	0.0	0.0
Range	-66.0 to 75.0	-52.0 to 46.0
QTcF interval (msec) N	287	270
Mean (SE)	-0.3 (1.90)	-0.3 (1.62)
Median	0.1	-1.5
Range	-365.9 to 200.1	-105.7 to 203.7
Heart rate (bpm) N	287	272
Mean (SE)	2.6 (0.52)	8.1 (0.64)
Median	2.0	8.0
Range	-24.0 to 31.0	-24.0 to 72.0

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Table 48. PCS Abnormal Values in at least 2 Subjects at Endpoint

ECG Parameter PCS abnormal value	Placebo N = 303		Trospium N = 298	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 ECG PCS abnormal value	96/287 (33.4)	67/287 (23.3)	78/274 (28.5)	52/272 (19.1)
PR Interval				
High: >200 msec only	12/286 (4.2)	6/272 (2.2)	9/262 (3.4)	2/240 (0.8)
High: Increase ≥ 20 msec only	19/286 (6.6)	19/272 (7.0)	12/262 (4.6)	12/240 (5.0)
High: >200 and Increase ≥ 20 msec	5/286 (1.7)	4/272 (1.5)	3/262 (1.1)	2/240 (0.8)
High: >200, Increase ≥ 20 msec or both	36/286 (12.6)	29/272 (10.7)	24/262 (9.2)	16/240 (6.7)
QRS Interval				
High: >100 msec only	36/287 (12.5)	8/251 (3.2)	29/274 (10.6)	5/235 (2.1)
High: Increase ≥ 10 msec only	16/287 (5.6)	16/251 (6.4)	17/274 (6.2)	17/235 (7.2)
High: >100 and Increase ≥ 10 msec	10/287 (3.5)	8/251 (3.2)	11/274 (4.0)	6/235 (2.6)
High: >100, Increase ≥ 10 msec or both	62/287 (21.6)	32/251 (12.7)	57/274 (20.8)	28/235 (11.9)
QT Interval				
High: Increase ≥ 60 msec only	5/287 (1.7)	5/285 (1.8)	3/272 (1.1)	3/270 (1.1)
High: >500, Increase ≥ 60 msec or both	5/287 (1.7)	5/285 (1.8)	3/272 (1.1)	3/270 (1.1)
QTcF Interval				
High: Increase ≥ 60 msec only	2/287 (0.7)	2/285 (0.7)	4/272 (1.5)	4/270 (1.5)
High: >500, Increase ≥ 60 msec or both	3/287 (1.0)	3/285 (1.1)	4/272 (1.5)	4/270 (1.5)
Heart Rate				
Low: < 50 bpm only	4/287 (1.4)	2/278 (0.7)	1/274 (0.4)	1/267 (0.4)
Low: Decrease ≥ 15 only	6/287 (2.1)	6/278 (2.2)	3/274 (1.1)	3/267 (1.1)
Low: < 50 bpm and Decrease ≥ 15	2/287 (0.7)	2/278 (0.7)	0/274 (0.0)	0/267 (0.0)
Low: < 50 bpm, Decrease ≥ 15 bpm or both	12/287 (4.2)	10/278 (3.6)	4/274 (1.5)	4/267 (1.5)
High: < 100 bpm and Increase ≥ 15	1/287 (0.3)	1/278 (0.4)	7/274 (2.6)	7/267 (2.6)
High: < 100 and Increase ≥ 15 bpm or 120 and Increase ≥ 15 bpm	1/287 (0.3)	1/278 (0.4)	7/274 (2.6)	7/267 (2.6)

n = total patients who met PCS criteria at any point post Baseline.
N = total patients who had a ECG recorded after Baseline
N at BL = normal at Baseline, the number of patients who met PCS criteria for ECG at any time point after Baseline, and whose Baseline ECG was normal
PCS = potentially clinically significant.

5.4.8 Safety Conclusions:

- The AE's reported in this study are generally consistent with those seen in other anticholinergic drugs in its class that are used to treat OAB.
- Nervous system events were rarely reported and were seen with a higher incidence in the placebo group.
- Cardiac and ECG-related events were rarely reported. Except for increased heart rate (seen in 1.3 % of subjects in the Sanctura XR group), there was no cardiac-related event seen in more than one Sanctura XR treated subject.
- There were no deaths in either treatment group.
- There were no SAE's judged possibly related to study drug.
- The incidence of discontinuation due to constipation, and dry mouth and urinary retention were 0 % and 1 %, and 0 % and 0.7 % for the placebo and trospium groups respectively.
- Except for constipation, for which the incidence of temporary interruption of study drug was 1 %, the overall incidence of TEAE's resulting in temporary interruption of study medication was similar between treatments groups.
- The mean and median changes from baseline to endpoint were similar between groups for all laboratory parameters.
- Physical examinations were unremarkable, and changes in vital signs from baseline to endpoint were as expected, with a slight increase in the pulse rate seen in the trospium group, consistent with that noted in the Phase-3 trials of trospium 20 mg BID.
- Changes from baseline to endpoint for ECG's were comparable between groups, with no clinically meaningful differences among groups.

6.0 Overall Conclusions

- Sanctura XR demonstrated a statistically significant ($p < 0.0001$) improvement (ie, decrease) in average number of daily toilet voids at Week 12 when compared with placebo. Patients treated with Sanctura XR experienced an average reduction from 12.8 voids per day at baseline to 10 toilet voids per day at Week 12.
- Sanctura XR demonstrated a statistically significant ($p=0.0022$) improvement (ie, decrease) in average number of UUI episodes per day at Week 12 compared with placebo. Patients treated with Sanctura XR experienced an average reduction from over 4 UUIs per day at baseline to less than 2 UUIs per day at Week 12.

Sanctura XR was well tolerated in this 12-week double-blind study. Compliance with study treatment and the completion rate of patients randomized was very good, and adverse events reported in this study were generally consistent with those events reported in other published studies of antimuscarinic compounds used to treat OAB. While constipation, dry mouth were the events reported with the highest incidence, the actual reported incidence for these events was lower than that had been observed in studies of trospium chloride 20 mg BID. There were no deaths and no treatment related serious adverse events in this study.

Sanctura XR was found to be well-tolerated, to have an acceptable safety profile, and to provide clinically and statistically significantly greater improvements in OAB symptoms when compared to placebo. This well-powered study of 601 OAB patients provides evidence that Sanctura XR has a comparable efficacy profile to that of the trospium chloride 20 mg BID formulation, and in many respects (specifically in terms of the incidence of TEAEs) may be superior to the 20 mg BID formulation for use in the treatment of patients with OAB.

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B. Study IP631-022

1.0 Introduction

Overactive bladder syndrome (OAB) is characterized by increased urinary urgency with or without urge urinary incontinence (UUI), usually with frequency and nocturia. OAB is estimated to affect 17 % of adults in the U.S. Hyperactivity of the detrusor muscle can result in bothersome symptoms of OAB that significantly affect overall quality of life.

The goal of pharmacotherapy is to inhibit urge symptoms and involuntary detrusor contractions by relaxing the bladder and increasing bladder capacity, thereby decreasing the number of voids per day. The inhibition of bladder contractility and stabilization of the detrusor muscle has been shown to be effected by agents that block acetylcholine at the muscarinic receptor site.

Anticholinergics are the agents most frequently used to treat OAB, and have demonstrated actions which decrease the number and amplitude of detrusor contractions, increase bladder capacity and improve the symptoms of urgency, frequency and UUI.

Trospium chloride (trospium) is a quaternary ammonium derivative of tropine with anticholinergic properties that has predominant peripheral antimuscarinic activity which antagonizes the effect of acetylcholine on cholinergically innervated organs and exhibits parasympatholytic action by reducing smooth muscle tone in the urogenital tract. This mechanism enables the detrusor to relax, leading to enhanced bladder compliance with increased capacity and control.

Trospium was first marketed in Germany in 1967 as a spasmolytic agent and received pan-European approval in the 1990's for specific indications including OAB. FDA approval of trospium 20 mg BID for the treatment of OAB occurred in May, 2004. This NDA submission proposes once daily (morning) dose of trospium 60 mg in an extended release capsule (Sanctura XR) for the same indication.

Clinical trials have demonstrated that trospium 20 mg BID reduced OAB symptoms and was generally well tolerated. The most-common AE's considered to be at least possibly related to treatment in two 12-week trials were dry mouth (20.1 %), constipation (9.6 %), compared to 8.7% and 9.7% respectively in this submission.

2.0 Study Objectives

The primary objective of this study was to evaluate the effects of a single daily AM dosing of Sanctura XR compared with placebo on OAB symptoms with predominant UUI including frequency, urgency severity, and UUI during a 12 week course.

3.0 Investigational Plan

3.1 Efficacy Variables

3.1.1 Primary Efficacy

The co-primary efficacy variables for both studies, based on urinary diary data collected over 3-days prior to baseline, and week 1, 4, and 12 visits were:

3. The change in number of toilet voids/day.
4. The change in UUI episodes frequency/day.

3.1.2 Secondary Efficacy

The secondary efficacy variables, also based on urinary diary data for 3 days prior to baseline and each double-blind visit were:

- UUI episodes frequency/week.
- Urgency severity with toilet voids.
- OAB symptom composite score/day.
- Urge frequency/day.
- “Dry rate” (no UUI episodes).
- Stress incontinence episodes frequency/day.
- Total incontinence episodes frequency/day.
- Total micturitions/day.
- Normal void frequency outcome.
- Complete responder rate outcome.

3.2 Study Design

The study was designed as parallel, randomized, double-blind, placebo-controlled trial of subjects with OAB having predominant UUI. The 12-week treatment was preceded by a baseline 3-day urinary diary for all subjects. A 7-day washout period was required for subjects currently taking OAB therapies. Subjects were randomized on a 1:1 basis to placebo or Sanctura XR once daily, and were stratified by the average number of voids /day, using the categories 10-15, 15-20, and > 20 average number of voids /day. Subjects were periodically evaluated during the 12-week course, and at study end, offered the option to continue into an open-label phase of the trial, with active drug, for an additional 9 months.

3.3 Dosing Schedule

Subjects were instructed to take a single capsule of study medication in the AM, at least 1 hour before meals, or on an empty stomach (unchewed), with water.

3.4 Study Population

Inclusion Criteria:

1. Male or female subjects \geq age 18.
2. OAB defined as:
 - Urinary frequency of \geq 30 toilet voids/3-days in baseline urinary diary;
 - Symptoms of urgency as recorded in baseline diary, ability to differentiate incontinence episodes;
 - Pure or mixed urinary incontinence with predominant UUI, and a minimum of 3 UUI episodes/baseline diary.
3. Symptoms of OAB \geq 6 months.
4. Ability to complete baseline diary, on-treatment assessments, and QOL scales.
5. Ability to use bathroom unassisted.
6. Informed consent.
7. Females of childbearing potential must have a negative pregnancy test prior to enrollment, not breastfeeding during study, and use accepted forms of birth control during study.

Exclusion Criteria:

1. Average total urine volume $>$ 3000 mL/day in baseline urinary diary.
2. Total average volume/void $>$ 250 mL in baseline urinary diary.
3. Subjects with predominant stress, insensate, or overflow incontinence.
4. History of neurogenic bladder.
5. Screening serum creatinine $>$ 1.5 mg/dL.
6. Cystic fibrosis in past year or active inflammatory bowel disease.
7. Uninvestigated hematuria.
8. UTI at screening, or recurrent UTI in past year.
9. Post-void residual urine volume $>$ 100 mL.
10. Subjects with indwelling catheter or requiring intermittent catheterization.
11. Bladder surgery within past 6 months, or past surgery with complications.
12. Subjects with interstitial cystitis, bladder cancer within past 6 months, or current therapy for bladder cancer.
13. PSA $>$ 4 ng/mL.
14. Treatment of OAB within 10 days prior to baseline.
15. Diuretics or estrogens not part of a long-term stable program.
16. Subjects employing bladder retraining/bladder drills program.
17. Subjects who are anticipated to begin or change non-medicinal bladder therapies during the course of study.
18. Prior pelvic malignancy with surgery leading to complications, or requiring radiation therapy.
19. History of myasthenia gravis or closed-angle glaucoma.

20. Hypersensitivity to atropine, oxybutinin, trospium, or excipients in study drug.

21. Any prior exposure to trospium, participation in another trial, or receiving

a non-approved drug less than 30 days prior to baseline.

22. Working 3rd or swing shift, or regularly waking after noon.

3.4.1 **Disposition of Subjects**

There were 69 study sites activated in the United States for this study, however subjects were enrolled at only 62 sites. Tables 1 and 2 summarize the primary screen failure reasons from screening/enrollment logs. Table 3 summarizes reasons for discontinuation from study.

Table 1. Subject Accounting

	Number of Subjects		
	Placebo	Sanctura XR	Total
Screened			1758
Enrolled	284	280	564
Completing N (% enrolled)	248 (87.3)	243 (86.8)	491 (87.0)
Discontinuation N (%)	36 (12.7)	37 (13.2)	73 (13.0)

Table 2. Percent of Screen Failures by Reason

Reason for Failure	Failure Percent
Failed entry criterion for urinary frequency average < 10/day	25 %
Failed entry criterion for UUI < 7/week	6 %
Total daily volume > 3000 mL/day	12 %
Investigator decision or subject schedule	7 %
Unable to correctly complete diary	2 %
Other medical conditions	12 %
Other reasons	36 %

Table 3. Reasons for Discontinuation

Reasons	Number (%) of Subjects	
	Placebo N=284	Sanctura XR N=280
Total	36 (12.7 %)	37 (13.2 %)
Discontinued		
Adverse event	8 (2.8 %)	18 (6.4%)
Protocol violation	2 (0.7)	1 (0.4 %)
Withdrawn consent	8 (2.8 %)	7 (2.5 %)

Non-compliance	1 (0.4)	1 (0.4 %)
Lost to follow-up	10 (3.5 %)	7 (2.5 %)
Other reason	7 (2.5 %)	1 (1.1 %)

3.5 Treatments

Following enrollment, eligible subjects were randomized to receive either Sanctura XR or matching placebo once daily upon arising, at least 1 hour before meals or on an empty stomach, un-chewed, with water, for up to 12 weeks of treatment. If a subject was unable to take the dose before noon on any day, the subjects was instructed to omit that day's dose and recommence daily dosing the following morning.

4.0 Integrated Review of Efficacy

4.1 Primary Efficacy Results

Sanctura XR met the 2 primary endpoints at all study visits.

- Sanctura XR demonstrated a statistically significant ($p < 0.0009$) decrease in average number of daily toilet voids (12.8/day at baseline to 10.3/day at Week 12) compared with placebo.
- Sanctura XR demonstrated a statistically significant ($p=0.0001$) decrease in average number of UUI episodes (> 4 UUIs/day at baseline to < 2 UUIs at Week 12) compared with placebo.

A total of 543 subjects (267 Sanctura XR and 276 placebo) were stratified by average number of baseline voids/day and then randomized 1:1. Subjects were predominantly female (87.7 %), White (82.4 %) and ages 21-90.

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Table 4 demonstrates the baseline characteristics of the treatment groups in this study.

Table 4. Demographic and Baseline Characteristics – Total Patient Sample

Baseline Characteristic	Placebo N=284	Sanctura XR N=280
Age		
Mean	54.4	61.2
Median (range)	58 (21-87)	62 (26-90)
Categories N (%)		
< 65	192 (67.6%)	168 (60.0%)
65- < 75	64 (22.5%)	69 (24.6%)
≥ 75	28 (9.9%)	43 (15.4%)
Gender N (%)		
Female	249 (87.7%)	230 (82.1%)
Male	35 (12.3%)	50 (17.9%)
Race N (%)		
White	234 (82.4%)	245 (87.5%)
Black	28 (9.9%)	18 (6.4%)
Hispanic	14 (4.9%)	12 (4.3%)
Asian	3 (1.1%)	2 (0.7%)
Other	5 (1.8%)	3 (1.1%)
Height in cm		
Mean	164.3	163.7
Weight in kg		
Mean	85.7	85.0
Prior anticholinergics for OAB, N(%)		
Naive	128 (45.1%)	138 (49.3%)
Non-naïve	156 (54.9%)	142 (50.7%)

Sanctura XR demonstrated an average reduction of toilet voids, from 12.8 voids/day at baseline to 10 voids/day at Week 12, compared with placebo ($p < 0.0001$). This is seen in Table 5, where a negative change indicates improvement.

Table 5. Change in Daily Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	12.94 (0.16)	12.84 (0.18)	0.2201
Change from Baseline	1	-1.15 (0.15)	-1.41 (0.16)	0.0789
	4	-1.71 (0.17)	-2.25 (0.15)	0.0047
	12	-1.80 (0.17)	-2.54 (0.19)	0.0009

Sanctura XR also demonstrated (secondary analyses) a 19 % average reduction in toilet voids from baseline to Week 12 compared with placebo ($p < 0.0002$), as seen in Table 6.

Table 6. Percent Change in Daily Toilet Voids

ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	12.94 (0.16)	12.84 (0.18)	0.2201
Change from Baseline	1	-8.26 (1.08)	-10.26 (1.17)	0.0528
	4	-12.48 (1.23)	-17.02 (1.26)	0.0016
	12	-13.13 (1.25)	-19.27 (1.34)	0.0002

Sanctura XR demonstrated a decrease in average number of diurnal and nocturnal toilet voids ($p=0.0004$), and a trend toward statistical significance ($p= 0.0900$) in decrease in average number of nocturnal voids at Week 12, compared with placebo. These results can be seen in Tables 7 and 8.

Table 7. Change in Diurnal Toilet Voids

ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	10.97 (0.16)	10.63 (0.17)	0.1097
Change from Baseline	1	-0.83 (0.14)	-0.95 (0.14)	0.3107
	4	-1.28 (1.16)	-1.53 (0.16)	0.0842
	12	-1.44 (0.14)	-2.12 (0.12)	0.0029

Table 8. Change in Nocturnal Toilet Voids

ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 261	N= 251	
Baseline	0	2.09 (0.07)	2.35 (0.09)	0.0484
Change from Baseline	1	-0.39 (0.07)	-0.52 (0.07)	0.2294
	4	-0.51 (0.07)	-0.80 (0.08)	0.0160
	12	-0.61 (0.07)	-0.89 (0.09)	0.0302

Sanctura XR demonstrated a decrease in average number of UUI episodes/day ($p < 0.0001$) and median percent change in number of UUI episodes/day ($p < 0.0001$) compared with placebo at Week 12, as seen in Tables 9 and 10.

Table 9. Change in UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	4.04 (0.20)	4.02 (0.18)	0.5304
Change from Baseline	1	-1.04 (0.15)	-1.70 (0.15)	<0.0001
	4	-1.51 (0.16)	-2.25 (0.16)	<0.0001
	12	-1.62 (0.17)	-2.35 (0.18)	<0.0001

Table 10. Median Percent Change in UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	3.00	3.33	0.1084
Change from Baseline	1	-28.6	-50.0	<0.0001
	4	-46.3	-71.4	0.0003
	12	-52.3	-83.3	<0.0001

Sanctura XR demonstrated a decrease in average percent change in number of diurnal and nocturnal UII episodes/day ($p < 0.0001$, and $p = 0.0504$ respectively) in number of UII compared with placebo at Week 12, as seen in Tables 11 and 12.

Table 11. Percent Change in Diurnal UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	3.43 (0.17)	3.34 (0.15)	0.6765
Change from Baseline	1	-21.2 (3.98)	-41.4 (3.64)	<0.0001
	4	-36.2 (3.90)	-56.8 (3.47)	<0.0001
	12	-35.7 (4.97)	-56.3 (4.53)	<0.0001

Table 12. Percent Change in Nocturnal UII Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 175	N= 175	
Baseline	0	1.00 (0.06)	1.06 (0.07)	0.6262
Change from Baseline	1	-30.1 (7.87)	-35.7 (7.90)	0.2468
	4	-41.9 (8.20)	-55.7 (6.41)	0.1864
	12	-47.6 (7.64)	-63.1 (6.27)	0.0504

4.2 Secondary Efficacy Results—Diary Data

Sanctura XR demonstrated a decrease in average number and median percent change in number of UUI episodes/week ($p < 0.0001$) at Week 12 compared with placebo, as seen in Tables 13 and 14.

Table 13. Change in UUI Episodes/Week ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	28.31 (1.37)	28.15 (1.24)	0.5401
Change from Baseline	1	-7.30 (1.03)	-11.89 (1.04)	<0.0001
	4	-10.58 (1.12)	-15.75 (1.14)	<0.0001
	12	-11.33 (1.20)	-16.43 (1.29)	<0.0001

Table 14. Median Percent Change in UUI Episodes/Week ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	21.00	23.33	0.1084
Change from Baseline	1	-28.6	-50.0	<0.0001
	4	-46.3	-71.4	0.0003
	12	-52.3	-83.3	<0.0001

Sanctura XR demonstrated a decrease in average urgency severity associated with daily toilet voids ($p=0.0004$) at Week 12 compared with placebo, as seen in Table 15.

Table 15. Change in Urgency Severity with Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	1.83 (0.03)	1.82 (0.03)	0.8459
Change from Baseline	1	-0.07 (0.02)	-0.16 (0.03)	0.0135
	4	-0.12 (0.03)	-0.28 (0.03)	<0.0001
	12	-0.13 (0.03)	-0.28 (0.03)	0.0003

Sanctura XR demonstrated a decrease in average diurnal and nocturnal urgency severity associated with daily toilet voids at Week 12 ($p=0.0003$ and $p= 0.0329$ respectively) compared with placebo, as seen in Tables 16 and 17.

Table 16. Change in Diurnal Urgency Severity with Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	1.79 (0.03)	1.78 (0.03)	0.9477
Change from Baseline	1	-0.07 (0.03)	-0.17 (0.03)	0.0121
	4	-0.11 (0.03)	-0.28 (0.03)	<0.0001
	12	-0.12 (0.03)	-0.28 (0.03)	0.0003

Table 17. Change in Nocturnal Urgency Severity with Toilet Voids ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 261	N= 249	
Baseline	0	2.05 (0.04)	2.06 (0.04)	0.8981
Change from Baseline	1	-0.01 (0.04)	-0.11 (0.04)	0.1871
	4	-0.09 (0.04)	-0.22 (0.05)	0.0259
	12	-0.06 (0.05)	-0.23 (0.05)	0.0329

Sanctura XR demonstrated a decrease in average and average percent change in OAB-SCS at Week 12 compared with placebo, as seen in Tables 18 and 19.

Table 18. Change in Daily OAB-SCS ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	37.09 (0.66)	36.75 (0.67)	0.6232
Change from Baseline	1	-4.09 (0.64)	-6.03 (0.60)	0.0017
	4	-6.33 (0.71)	-9.31 (0.68)	0.0002
	12	-6.49 (0.73)	-9.84 (0.75)	0.0002

Table 19. Percent Change in Daily OAB-SCS ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	37.09 (0.66)	36.75 (0.67)	0.6232
Change from Baseline	1	-9.23 (1.45)	-15.27 (1.47)	0.0009
	4	-15.10 (1.64)	-24.48 (1.61)	<0.0001
	12	-15.33 (1.74)	-26.14 (1.78)	<0.0001

Sanctura XR demonstrated an increase in average volume and average percent change in volume voided/toilet void at Week 12 ($p=0.0014$ and $p=0.0012$ respectively) compared with placebo, as seen in Tables 20 and 21.

Table 20. Change in Daily Volume Voided/Toilet Void ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 266	
Baseline	0	151.83 (2.84)	149.61 (2.94)	0.7298
Change from Baseline	1	11.94 (2.53)	24.08 (2.35)	<0.0001
	4	19.57 (3.12)	29.29 (2.97)	0.0020
	12	17.78 (3.27)	31.53 (3.39)	0.0014

Table 21. Percent Change in Daily Volume Voided/Toilet Void ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 266	
Baseline	0	151.83 (2.84)	149.61 (2.94)	0.7298
Change from Baseline	1	9.69 (1.97)	19.10 (1.99)	<0.0001
	4	14.96 (2.41)	23.14 (2.48)	0.0008
	12	14.49 (2.50)	24.77 (2.70)	0.0012

Sanctura XR demonstrated a decrease in average daily number of urge frequency episodes at Week 12 compared with placebo ($p = 0.0010$), as seen in Table 22.

Table 22. Change in Daily Urge Frequency Associated with Toilet Voids, LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	11.92 (0.18)	11.66 (0.20)	0.2385
Change from Baseline	1	-1.18 (0.17)	-1.46 (0.18)	0.0758
	4	-1.73 (0.20)	-2.48 (0.21)	0.0014
	12	-1.85 (0.21)	-2.80 (0.22)	0.0010

Sanctura XR was superior to placebo ($p = 0.0001$) with respect to percent of subjects completely dry at Week 12, as seen in Table 23.

Table 23. Number (%) of Subjects Dry for UI: CMH Test ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
Toilet voids		N= 276	N= 267	
Baseline	0	0	0	N/A
Change from Baseline	1	26 (9.5%)	43 (16.1%)	0.0191

	4	48 (17.4%)	78 (29.2%)	0.0013
	12	58 (21.0%)	95 (35.6%)	0.0010

Sanctura XR failed to demonstrate either a statistical or numerical decrease in the average number of stress incontinence episodes/day compared with placebo, as seen in Table 24.

Table 24. Change in Stress Incontinence Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 109	N= 131	
Baseline	0	1.37 (0.12)	1.35 (0.10)	0.7555
Change from Baseline	1	-0.42 (0.12)	-0.35 (0.13)	0.9866
	4	-0.63 (0.12)	-0.62 (0.13)	0.6079
	12	-0.55 (0.11)	-0.83 (0.11)	0.0258

Sanctura XR demonstrated a decrease in average number of total urinary incontinence episodes per day at Week 12 compared with placebo ($p < 0.0001$), as seen in Table 25.

Table 25. Change in Total Urinary Incontinence Episodes/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	4.59 (0.23)	4.68 (0.20)	0.2256
Change from Baseline	1	-1.15 (0.16)	-1.84 (0.16)	<0.0001
	4	-1.69 (0.18)	-2.52 (0.18)	<0.0001
	12	-1.78 (0.18)	-2.74 (0.21)	<0.0001

Sanctura XR demonstrated a decrease in average number of total micturitions per day at Week 12 compared with placebo ($p < 0.0001$), as seen in Table 26.

Table 26. Change in Average (SE) Total Micturitions/Day ITT:LOCF

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	13.02 (0.16)	12.96 (0.18)	0.2952
Change from Baseline	1	-1.18 (0.16)	-1.49 (0.16)	0.0414
	4	-1.77 (0.18)	-2.33 (0.18)	0.0045
	12	-1.86 (0.18)	-2.61 (0.19)	0.0010

Sanctura XR was superior to placebo (p=0.0008) in the percent of subjects with a normal void frequency (\leq voids/day) at week 12, as seen in Table 27.

Table 27. Number (%) of Subjects with \leq 8 Voids/Day **ITT:LOCF**

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	0	0	N/A
On-Treatment	1	22 (8.0)	31 (11.7%)	0.1282
	4	37 (13.4%)	59 (22.1%)	0.0069
	12	44 (15.9%)	74 (27.7%)	0.0008

Sanctura XR was superior to placebo (p=0.0013) in percent of subjects completely responding (no UUI episodes and \leq 8 voids/day) at week 12, as seen in Table 28.

Table 28. Number (%) of Complete Responders **ITT:LOCF**

	Week	Placebo	Sanctura XR	P-Value
		N= 276	N= 267	
Baseline	0	0	0	N/A
On-Treatment	1	11 (4.0%)	20 (7.5%)	0.0654
	4	24 (8.7%)	48 (18%)	0.0014
	12	31 (11.2%)	57 (21.3%)	0.0013

4.3 Other Efficacy Endpoints

In the Kings Health Questionnaire, the Sanctura XR group improvement over placebo (p < 0.05) was noted in all domains except Emotions and General Health Perceptions, as seen in Table 29.

Table 29. KHQ Domain at Baseline and Week 12—Average (SE) **ITT:LOCF**

Domain	Time Point	Week	Placebo N=267	Sanctura XR N=257	p-Value
General Health Perception	Baseline	0	31.50 (0.83)	32.41 (0.93)	0.3113
	Change	12	-2.94 (0.91)	-4.50 (0.99)	0.2277
Incontinence Impact	Baseline	0	79.95 (1.30)	78.61 (1.45)	0.6695
	Change	12	-15.91 (1.90)	-23.36 (1.95)	0.0178
Role Limitations	Baseline	0	61.03 (1.52)	61.07 (1.60)	0.8308
	Change	12	-15.06 (1.85)	-26.04 (1.95)	<0.0001
Physical Limitations	Baseline	0	60.00 (1.54)	59.54 (1.68)	0.8692
	Change	12	15.67 (1.93)	-26.67 (2.10)	0.0001

Social Limitations	Baseline	0	40.27 (1.63)	40.62 (1.75)	0.8592
	Change	12	-11.20 (1.60)	-16.76 (1.71)	0.0086
Personal Relationships	Baseline	0	53.42 (2.13)	56.51 (2.37)	0.3610
	Change	12	-11.49 (2.04)	-18.34 (2.22)	0.0247
Emotions	Baseline	0	43.56 (1.65)	46.44 (1.88)	0.3931
	Change	12	-15.74 (1.66)	-21.00 (1.95)	0.0899
Sleep/Energy	Baseline	0	56.16 (1.66)	56.18 (1.66)	0.9671
	Change	12	-14.52 (1.65)	-21.03 (1.78)	0.0237
Severity	Baseline	0	33.95 (0.42)	33.38 (0.45)	0.4434
	Change	12	-8.43 (0.61)	-12.21 (0.62)	<0.0001

As seen in Table 30, the Sanctura XR group demonstrated a statistically significant ($p < 0.02$) improvement over placebo in the OABq HRQL total score and in the domains of Concern/ Worry, Coping, and Sleep.

Table 30. HRQL Domain at Week 12--- Average (SE) ITT:LOCF

Domain	Time Point	Week	Placebo N=292	Sanctura XR N=278	p-Value
HRQL Total Score	Baseline	0	53.90 (1.24)	54.03 (1.32)	0.7910
	Change	12	17.68 (1.45)	24.10 (1.52)	0.0010
Concerns/ Worry	Baseline	0	47.74 (1.40)	47.81 (1.56)	0.8949
	Change	12	21.54 (1.66)	29.43 (1.64)	0.0007
Coping	Baseline	0	48.49 (1.44)	50.79 (1.50)	0.2610
	Change	12	18.41 (1.66)	24.66 (1.70)	0.0027
Social Interactions	Baseline	0	77.21 (1.37)	76.11 (1.51)	0.7821
	Change	12	10.58 (1.31)	13.33 (1.43)	0.1839
Sleep	Baseline	0	50.17 (1.59)	50.21 (1.59)	0.8914
	Change	12	16.99 (1.68)	22.71 (1.78)	0.0155

The Sanctura XR group demonstrated an improvement over placebo ($p < 0.04$) in all of the Symptom Bother and Symptom Bother/Severity scales, as seen in Table 31.

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Table 31. OABq Quality of Life Questionnaire - Symptom Bother Scales at Baseline and Change from Baseline to Week 12: Average (SE) and Rank Analysis of Variance – ITT:LOCF

Domain	Time Point	Placebo N=267	Sanctura XR N=258	P-Value
Total Symptom Bother/Severity Score	Baseline	64.87 (1.04)	63.50 (1.12)	0.4702
	Change from Baseline	-21.08 (1.53)	-30.43 (1.56)	<0.0001
Frequent Urination During Daytime	Baseline	4.62 (0.05)	4.53 (0.06)	0.6209
	Change from Baseline	-1.13 (0.09)	-1.60 (0.09)	0.0007
An Uncontrollable Urge to Urinate	Baseline	4.34 (0.07)	4.25 (0.07)	0.4629
	Change from Baseline	-1.08 (0.09)	-1.57 (0.09)	0.0002
Sudden Urge to Urinate Without Warning	Baseline	4.35 (0.07)	4.27 (0.08)	0.7588
	Change from Baseline	-1.22 (0.09)	-1.71 (0.11)	0.0005
Accidental Loss of Small Amounts of Urine	Baseline	4.07 (0.08)	4.01 (0.09)	0.7237
	Change from Baseline	-0.95 (0.10)	-1.52 (0.10)	0.0002
Night Time Urination	Baseline	4.06 (0.09)	3.95 (0.09)	0.2792
	Change from Baseline	-0.88 (0.10)	-1.14 (0.10)	0.3020
Waking at Night for Need to Urinate	Baseline	4.19 (0.08)	4.12 (0.09)	0.5512
	Change from Baseline	-0.93 (0.09)	-1.30 (0.10)	0.0065
Urine Loss with a Strong Desire to Urinate	Baseline	4.10 (0.08)	4.08 (0.08)	0.9015
	Change from Baseline	-1.09 (0.10)	1.68 (0.10)	<0.0001

5.0 Efficacy Conclusions

- Sanctura XR demonstrated a statistically significant ($p = 0.0009$) improvement (ie, decrease) in average number of daily toilet voids at Week 12 when compared with placebo. Patients treated with Sanctura XR experienced an average reduction from 12.8 voids per day at baseline to 10.3 toilet voids per day at Week 12. In addition, Week 4 outcomes were statistically significant and Week 1 outcomes demonstrated a trend toward significance.
- Sanctura XR demonstrated a statistically significant ($p < 0.0001$) improvement (ie, decrease) in average number of UUI episodes per day at Week 12 when compared with placebo. Patients treated with Sanctura XR experienced an average reduction from over 4 UUIs per day at baseline to less than 2 UUIs per day at Week 12. In addition, Week 4 and Week 1 outcomes were also statistically significant.

The Sanctura XR demonstrated statistically significantly greater improvement in toilet voids at Weeks 4 and 12 and for UUI's, urgency severity associated with toilet voids, and volume voided per toilet void compared with placebo at Week 12 as well as at Weeks 4 and 1. It is important to note the internal consistency of the secondary efficacy analyses were all in favor of the Sanctura group which provides further support for the results of the primary efficacy analyses.

6.0 Integrated Review of Safety

Brief Statement of Conclusions

The adverse events associated with this formulation of Sanctura XR appears to be similar to that seen with other anticholinergics used to treat OAB. Dry mouth and constipation were the AE's reported with the highest incidence (approximately 9%) which was lower than that seen with 20 mg BID regimen. Except for urinary tract infections that were reported in 7 % of subjects and other AE's were seldom reported. When the investigator judged relationship of UTI to study drug, the incidence decreased to 1.2 %. **There were no deaths in any treatment group.**

6.1 **Extent of Exposure**

The average duration of exposure to the double-blind medication is summarized in Table 32.

Table 32. Duration of Exposure (Days)

	Placebo N = 284	Trospium N = 280
Number of patients with exposure information ^a	N = 275	N = 269
Mean (SE)	78.6 (1.13)	79.7 (1.09)
Median	84	84
Range (minimum to maximum)	1 - 94	2 - 104

a Some patients did not have last dose date of study medication reported and are not included in this table.
SE = standard error

6.2 Adverse Events

Treatment-emergent AE's (TEAEs) reported in 2% or more subjects in either treatment group is presented in Table 33 by preferred term in decreasing order of frequency based on trospium incidence.

Table 33. TEAEs Reported in at Least 2% of Subjects in Either Group

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Total patients with at least 1 TEAE	130 (45.8)	154 (55.0)
Dry mouth	13 (4.6)	38 (13.6)
Urinary tract infection	17 (6.0)	24 (8.6)
Constipation	5 (1.8)	23 (8.2)
Headache	9 (3.2)	15 (5.4)
Nausea	10 (3.5)	12 (4.3)
Nasopharyngitis	4 (1.4)	12 (4.3)
Influenza	4 (1.4)	8 (2.9)
Flatulence	3 (1.1)	8 (2.9)
Diarrhoea	8 (2.8)	7 (2.5)
Dry eye	1 (0.4)	6 (2.1)
Abdominal pain	1 (0.4)	6 (2.1)
Upper respiratory tract infection	7 (2.5)	5 (1.8)

Table 34 presents the most frequently reported TEAE's by age subgroups.

Table 34. **Incidence of TEAE'S by Preferred Term and Age Subgroups**

MedDRA Preferred term	Number of patients (%)			
	Placebo N = 284		Trospium N = 280	
	< 65 years (N=192)	≥ 65 years (N=92)	< 65 years (N=168)	≥ 65 years (N=112)
Total patients with at least 1 TEAE	99 (51.6)	31 (33.7)	92 (54.8)	62 (55.4)
Dry Mouth	10 (5.2)	3 (3.3)	18 (10.7)	20 (17.9)
Urinary tract infection	12 (6.3)	5 (5.4)	7 (4.2)	17 (15.2)
Constipation	2 (1.0)	3 (3.3)	9 (5.4)	14 (12.5)
Headache	7 (3.6)	2 (2.2)	11 (6.5)	4 (3.6)

TEAE = treatment-emergent adverse event.

TEAE's categorized by severity are seen in Table 35.

Table 35. **Incidence of TEAEs by Severity**

TEAE severity	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Total patients with at least 1 TEAE	130 (45.8)	154 (55.0)
Mild	60 (21.1)	67 (23.9)
Moderate	59 (20.8)	67 (23.9)
Severe	11 (3.9)	20 (7.1)

A summary of the incidence of severe TEAE's in at least 2 trospium subjects are presented in Table 36.

Table 36. **Incidence of Severe TEAE's by Preferred Term**

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Total patients with at least 1 severe TEAE ^a	11 (3.9)	20 (7.1)
Dry mouth	0 (0.0)	3 (1.1)
Abdominal pain	0 (0.0)	2 (0.7)
Urinary tract infection	0 (0.0)	2 (0.7)

^a A patient may have experienced more than 1 severe TEAE, but is counted once in the total number of patients with a severe TEAE.

Table 37 presents a list of the incidence of TEAE's of interest.

Table 37. TEAE's of Interest by Preferred Term

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Total patients with at least 1 TEAE	130 (45.8)	154 (55.0)
Dry mouth	13 (4.6)	38 (13.6)
Urinary tract infection	17 (6.0)	24 (8.6)
Constipation	5 (1.8)	23 (8.2)
Headache	9 (3.2)	15 (5.4)
Dry eye	1 (0.4)	6 (2.1)
Rash	2 (0.7)	3 (1.1)
Dizziness	4 (1.4)	2 (0.7)
Tachycardia	2 (0.7)	2 (0.7)
Ischaemic Stroke	0 (0.0)	2 (0.7)
Urinary retention	1 (0.4)	1 (0.4)
Blurred vision	0 (0.0)	1 (0.4)
QT Interval Prolonged	0 (0.0)	1 (0.4)
Myocardial ischemia	1 (0.4)	0 (0.0)

TEAEs judged by investigator to be at least possibly related to study treatment in at least 1% of subjects in either group are seen in Table 38 in decreasing frequency based on rates in the trospium group.

Table 38. Incidence of Possibly Related TEAEs in at Least 1% of Subjects

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Total patients with at least 1 TEAE	130 (45.8)	154 (55.0)
Dry mouth	13 (4.6)	38 (13.6)
Urinary tract infection	17 (6.0)	24 (8.6)
Constipation	5 (1.8)	23 (8.2)
Headache	9 (3.2)	15 (5.4)
Dry eye	1 (0.4)	6 (2.1)
Rash	2 (0.7)	3 (1.1)
Dizziness	4 (1.4)	2 (0.7)
Tachycardia	2 (0.7)	2 (0.7)
Ischaemic Stroke	0 (0.0)	2 (0.7)
Urinary retention	1 (0.4)	1 (0.4)
Blurred vision	0 (0.0)	1 (0.4)
QT Interval Prolonged	0 (0.0)	1 (0.4)
Myocardial ischemia	1 (0.4)	0 (0.0)

Deaths, Other SAE's, and Other Significant AE's

No subject died during this study. The incidence of all treatment-emergent SAEs is seen in Table 39. There were one SAE's judged as a "remote relationship to study treatment".

Table 39. Incidence of All Treatment-Emergent SAE's

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Total patients with at least 1 TEAE	130 (45.8)	154 (55.0)
Total patients with at least 1 Treatment-emergent SAE	5 (1.8)	5 (1.8)
Coronary artery disease	1 (0.4)	0 (0.0)
Small intestinal obstruction	0 (0.0)	1 (0.4)
Pneumonia	0 (0.0)	1 (0.4)
Pulmonary sepsis	0 (0.0)	1 (0.4)
Diarrhoea infectious	1 (0.4)	0 (0.0)
Diverticulitis	1 (0.4)	0 (0.0)
Staphylococcal infection	1 (0.4)	0 (0.0)
Viral upper respiratory tract infection	1 (0.4)	0 (0.0)
Upper limb fracture	0 (0.0)	1 (0.4)
Ischaemic Stroke	0 (0.0)	2 (0.7)
Pneumonia Aspiration	0 (0.0)	1 (0.4)
Asthma	2 (0.7)	0 (0.0)

As seen in the above Table 39, few subjects experienced an "other significant" AE, and the treatments groups were comparable in these instances. No subjects required a dose reduction.

The incidence of Other Significant TEAE's by criterion is seen in Table 40.
Table 40.

Other significant TEAE criterion	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Led to discontinuation of study medication	8 (2.8)	18 (6.4)
Led to temporary interruption of study medication	8 (2.8)	8 (2.9)
Required dose reduction of study medication	0	0

The incidence of AE's leading to discontinuation of study drug is seen in Table 41.

Table 41. TEAE's Leading to Study Drug Discontinuation

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 284	Trosipium N = 280
Total patients with at least 1 TEAE	130 (45.8)	154 (55.0)
Total patients with at least 1 TEAE leading to discontinuation of study medication	8 (2.8)	18 (6.4)
Constipation	1 (0.4)	3 (1.1)
Ischaemic stroke	0 (0.0)	2 (0.7)
Headache	1 (0.4)	2 (0.7)
Dry mouth	0 (0.0)	2 (0.7)
Abdominal pain upper	0 (0.0)	2 (0.7)
Urinary retention	0 (0.0)	1 (0.4)
Small intestinal obstruction	0 (0.0)	1 (0.4)
Renal pain	0 (0.0)	1 (0.4)
Non-cardiac chest pain	0 (0.0)	1 (0.4)
Nausea	0 (0.0)	1 (0.4)
Loose stools	0 (0.0)	1 (0.4)
Hypertension	1 (0.4)	1 (0.4)
Flatulence	1 (0.4)	1 (0.4)
Dyspnoea	0 (0.0)	1 (0.4)
Dry throat	0 (0.0)	1 (0.4)
Dry skin	0 (0.0)	1 (0.4)
Dry eye	0 (0.0)	1 (0.4)
Constipation aggravated	0 (0.0)	1 (0.4)
Back pain	0 (0.0)	1 (0.4)
Abdominal pain	0 (0.0)	1 (0.4)
Abdominal distension	0 (0.0)	1 (0.4)
Prostate cancer (men only)	1 (2.9)	0 (0.0)
Oedema peripheral	2 (0.7)	0 (0.0)
Genital rash	1 (0.4)	0 (0.0)
Coronary artery disease	1 (0.4)	0 (0.0)
Blood thyroid stimulating hormone increased	1 (0.4)	0 (0.0)

AE's leading to temporary interruption of study drug are seen in Table 42.

Table 42. Incidence of TEAE's Leading to Study Drug Interruption

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 284	Trospium N = 280
Total patients with at least 1 TEAE	130 (45.8)	154 (55.0)
Total patients with at least 1 TEAE where the study medication was temporarily interrupted	8 (2.8)	8 (2.9)
Dry mouth	0 (0.0)	2 (0.7)
Dry eye	0 (0.0)	1 (0.4)
Constipation	0 (0.0)	1 (0.4)
Faeces hard	0 (0.0)	1 (0.4)
Food poisoning	1 (0.4)	1 (0.4)
Nausea	2 (0.7)	1 (0.4)
Vomiting	1 (0.4)	1 (0.4)
Oedema peripheral	0 (0.0)	1 (0.4)
Gastroenteritis viral	1 (0.4)	1 (0.4)
Pneumonia	0 (0.0)	1 (0.4)
Skin bacterial infection	0 (0.0)	1 (0.4)
Decreased appetite	0 (0.0)	1 (0.4)
Lethargy	0 (0.0)	1 (0.4)
Nasal dryness	0 (0.0)	1 (0.4)
Pharyngolaryngeal pain	0 (0.0)	1 (0.4)
Sneezing	0 (0.0)	1 (0.4)
Diarrhoea	1 (0.4)	0 (0.0)
Stomach discomfort	1 (0.4)	0 (0.0)
Pyrexia	1 (0.4)	0 (0.0)
Diarrhoea infectious	1 (0.4)	0 (0.0)
Gastroenteritis	1 (0.4)	0 (0.0)
Oral candidiasis	1 (0.4)	0 (0.0)
Urinary tract infection	1 (0.4)	0 (0.0)
Asthma	1 (0.4)	0 (0.0)

5.3 Clinical Laboratory Evaluations

5.31 Potentially Clinically Significant (PCS) Hematology Values are seen in Table 43.

Table 43. Abnormal Values Reported in at least 2 Subjects at Endpoint

Hematology PCS abnormal value	Placebo N = 284		Trospium N = 280	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Hematology PCS abnormal value	8/264 (3.0)	5/263 (1.9)	3/258 (1.2)	2/258 (0.8)
WBC High ($\geq 16.0 \times 10^3 / \text{mm}^3$)	2/264 (0.8)	1/262 (0.4)	0/258 (0.0)	0/257 (0.0)
Eosinophils High ($\geq 10\%$)	2/264 (0.8)	2/262 (0.8)	1/258 (0.4)	0/256 (0.0)
RBC High (F: $\geq 6.0 \times 10^6 / \text{mm}^3$ M: $\geq 6.5 \times 10^6 / \text{mm}^3$)	2/264 (0.8)	1/261 (0.4)	0/258 (0.0)	0/258 (0.0)
Hematocrit Low (F: $\leq 2\%$ M: $\leq 37\%$)	2/264 (0.8)	1/262 (0.4)	2/258 (0.8)	1/255 (0.4)
Hemoglobin Low (F: ≤ 9.5 g/dL M: ≤ 11.5 g/dL)	1/264 (0.4)	0/262 (0.0)	2/258 (0.8)	2/258 (0.8)

n = total patients who met PCS criteria at endpoint after baseline.
N = total patients who had laboratory values for the analyte at any point after baseline (including patients who had a missing value at baseline).
N at BL = normal at baseline, the number of patients who met PCS criteria for the analyte at endpoint after Baseline and whose Baseline value was normal.
PCS = potentially clinically significant. F=female. M=male

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Serum chemistry PCS abnormal values at endpoint are summarized for all parameters reported in at least 2 subjects in either treatment group are seen in Table 44.

Table 44. PCS Abnormal Serum Chemistry Values

Chemistry PCS abnormal value	Placebo N = 284		Trospium N = 280	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Chemistry PCS abnormal value	24/266 (9.0)	17/266 (6.4)	42/263 (16.0)	27/263 (10.3)
Urea Nitrogen (BUN) High (≥ 30 mg/dL)	6/266 (2.3)	5/261 (1.9)	10/262 (3.8)	6/256 (2.3)
Uric Acid High (F ≥ 8.5 M: ≥ 10.5 mg/dL)	5/266 (1.9)	3/264 (1.1)	6/262 (2.3)	4/257 (1.6)
Bilirubin - Direct High (≥ 0.5 mg/dL)	3/266 (1.1)	1/262 (0.4)	3/262 (1.1)	1/257 (0.4)
Bilirubin - Total High (≥ 2 mg/dL)	1/266 (0.4)	1/265 (0.4)	2/262 (0.8)	0/260 (0.0)
Glucose High (>250 mg/dL)	2/266 (0.8)	2/265 (0.8)	3/262 (1.1)	2/257 (0.8)
Triglycerides High (>600 mg/dL)	2/266 (0.8)	2/263 (0.8)	3/263 (1.1)	0/260 (0.0)
HDL Low (≤ 30 mg/dL)	3/266 (1.1)	2/264 (0.8)	11/263 (4.2)	8/259 (3.1)
LDL High (≥ 200 mg/dL)	3/266 (1.1)	1/259 (0.4)	3/263 (1.1)	1/258 (0.4)
Calcium Low (<8.2 mg/dL)	1/266 (0.4)	1/265 (0.4)	2/262 (0.8)	2/257 (0.8)
Bicarbonate High (≥ 35 mmol/L)	1/266 (0.4)	1/262 (0.4)	3/262 (1.1)	3/258 (1.2)

n = total patients who met PCS criteria at any point after Baseline.

N = total patients who had laboratory values for the analyte at Endpoint after Baseline (including patients who had a missing value at Baseline).

N at BL = normal at Baseline, the number of patients who met PCS criteria for the analyte at Endpoint after Baseline and whose Baseline value was normal.

PCS = potentially clinically significant. F=female. M=male.

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Urinalysis PCS abnormal values at endpoint are summarized for all parameters reported in at least 2 subjects in either treatment group are seen in Table 45.

Table 45. Urinalysis: PCS Abnormal Values Reported in at least 2 Subjects at Endpoint

Urinalysis PCS abnormal value	Placebo N = 284		Trospium N = 280	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Urinalysis PCS abnormal value	66/266 (24.8)	60/266 (22.6)	76/264 (28.8)	60/264 (22.7)
Blood High (≥ 3+)	1/266 (0.4)	1/264 (0.4)	5/264 (1.9)	4/262 (1.5)
RBC/HPF High [(11-20)(21-40)(TNTC) /HPF]	6/266 (2.3)	5/264 (1.9)	6/264 (2.3)	3/257 (1.2)
WBC/HPF High [(11-20)(21-40)(TNTC) /HPF]	17/266 (6.4)	15/259 (5.8)	20/264 (7.6)	14/251 (5.6)
Hyaline Casts / LPF High [(3-20)(>20)(TNTC) /LPF]	2/266 (0.8)	2/264 (0.8)	2/264 (0.8)	2/263 (0.8)
Epithelial Cells / HPF High [(>20)(TNTC)]	11/266 (4.1)	11/258 (4.3)	12/264 (4.5)	12/252 (4.8)
Squamous Epith Cells / HPF High [(>20)(TNTC)]	21/266 (7.9)	21/252 (8.3)	18/264 (6.8)	16/249 (6.4)
Bacteria / HPF High [(21-40)(TNTC)]	21/266 (7.9)	21/252 (8.3)	18/264 (6.8)	16/249 (6.4)
Amorphous Sediment / HPF High (TNTC)	18/266 (6.8)	16/239 (6.7)	19/264 (7.2)	15/238 (6.3)
Calcium Oxalate Crystals / HPF High [(>20)(TNTC)]	14/266 (5.3)	12/252 (4.8)	12/264 (4.5)	10/254 (3.9)
Uric Acid Crystals / HPF High [(>20)(TNTC)]	1/266 (0.4)	1/263 (0.4)	4/264 (1.5)	3/260 (1.2)
Ammonium Urates / HPF High [(>20)(TNTC)]	0/266 (0.0)	0/266 (0.0)	2/264 (0.8)	2/264 (0.8)

n = total patients who met PCS criteria at any point after Baseline.
N = total patients who had laboratory values for the analyte at Endpoint after Baseline (including patients who had a missing value at Baseline).
N at BL = normal at Baseline, the number of patients who met PCS criteria for the analyte at Endpoint after Baseline and whose Baseline value was normal.
Epith = epithelial, HPF = high-powered field, PCS = potentially clinically significant, TNTC=too numerous to count
RBC = red blood cells, WBC = white blood cells

5.4 Vital Signs, Physical Findings and Other Observations Related to Safety

5.4.1 Pulse

Descriptive statistics for pulse recorded at baseline and endpoint are summarized in Table 46.

Table 46.

Pulse at Baseline and Endpoint

		Placebo N = 272	Trospium N = 266
Baseline	Mean (SE)	73.2 (0.57)	71.5 (0.63)
	Median	72	72
	Range	51 – 100	50 – 120
Endpoint	Mean (SE)	73.7 (0.56)	74.9 (0.63)
	Median	72	73
	Range	52 – 104	53 – 116
Change	Mean (SE)	0.5 (0.50)	3.4 (0.58)
	Median	2	2
	Range	-25 to 28	-40 to 36

SE=Standard Error

Blood Pressure and the vital signs PCS abnormal values (noted at any time) in at least 2 subjects are summarized in Table 47.

Table 47. Vital Signs: High or Low PCS Abnormal Values

Vital Sign Parameter	Placebo N = 284		Trospium N = 280	
	PCS (%) n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Systolic blood pressure:				
Low: < 90 or decrease \geq 20 mm Hg	31/272 (11.4)	31/272 (11.4)	25/269 (9.3)	25/266 (9.4)
High: >180 or increase \geq 20 mm Hg	23/272 (8.5)	23/272 (8.5)	29/269 (10.8)	29/266 (10.9)
Diastolic blood pressure:				
Low: < 50 or decrease \geq 15 mm Hg	20/272 (7.4)	20/272 (7.4)	17/269 (6.3)	17/266 (6.4)
High: >105 or increase \geq 15 mm Hg	19/272 (7.0)	19/272 (7.0)	16/269 (5.9)	16/266 (6.0)
Pulse				
Low: <50 bpm, Decrease \geq 15 bpm, or both	20/272 (7.4)	20/272 (7.4)	10/269 (3.7)	10/266 (3.7)
High: >100 and Increase \geq 15 bpm or >120 and Increase <15 bpm	1/272 (0.4)	1/272 (0.4)	6/269 (2.2)	6/266 (2.3)

n = total patients who met PCS criteria at any point, post baseline.
N = total patients who had a vital sign measurement recorded after baseline (including patients who had a missing value at baseline)
N at BL = normal at baseline, the number of patients who met PCS criteria for the vital signs at any time point after baseline, and whose baseline vital signs were normal
PCS = potentially clinically significant

5.4.2 Descriptive statistics by ECG parameters are summarized in Tables 48 and 49.

Table 48. Heart Rate and Changes in QT and QTcF Intervals

ECG Parameter	Placebo N = 284	Trospium N = 280
PR interval (msec) N	260	257
Mean (SE)	-1.4 (0.88)	-0.7 (2.65)*
Median	0.0	-2.0*
Range	-48.0 to 68.0	-130.0 to 584.0*
QRS interval (msec) N	264	260
Mean (SE)	0.7 (0.45)	-0.3 (0.70)
Median	0.0	0.0
Range	-20.0 to 61.0	-80.0 to 56.0
QTcF interval (msec) N	264	260
Mean (SE)	-2.2 (1.42)	-2.8 (1.86)
Median	-2.2	-1.4
Range	-188.9 to 82.7	-200.9 to 201.3
Heart rate (bpm) N	264	260
Mean (SE)	-0.1 (0.58)	4.2 (0.63)
Median	0.0	4.0
Range	-32.0 to 40.0	-29.0 to 36.0

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Table 49. PCS Abnormal Values in at least 2 Subjects at Endpoint

ECG Parameter PCS abnormal value	Placebo N = 284		Trospium N = 280	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 ECG PCS abnormal value	64/264 (24.2)	48/264 (18.2)	82/261 (31.4)	55/260 (21.2)
PR Interval				
High: >200 msec only	7/261 (2.7)	1/248 (0.4)	10/259 (3.9)*	0/241 (0.0)*
High: Increase ≥ 20 msec only	12/261 (4.6)	12/248 (4.8)	15/259 (5.8)*	15/241 (6.2)*
High: >200 and Increase ≥ 20 msec	1/261 (0.4)	1/248 (0.4)	4/259 (1.5)*	4/241 (1.7)*
High: >200, Increase ≥ 20 msec or both	20/261 (7.7)	14/248 (5.6)	29/259 (11.2)*	19/241 (7.9)*
QRS Interval				
High: >100 msec only	15/264 (5.7)	2/240 (0.8)	26/261 (10.0)	4/225 (1.8)
High: Increase ≥ 10 msec only	13/264 (4.9)	13/240 (5.4)	16/261 (6.1)	16/225 (7.1)
High: >100 and Increase ≥ 10 msec	7/264 (2.7)	5/240 (2.1)	9/261 (3.4)	6/225 (2.7)
High: >100, Increase ≥ 10 msec or both	35/264 (13.3)	20/240 (8.3)	51/261 (19.5)	26/225 (11.6)
QT Interval				
High: Increase ≥ 60 msec only	4/264 (1.5)	4/263 (1.5)	3/261 (1.1)	3/258 (1.2)
High: >500, Increase ≥ 60 msec or both	4/264 (1.5)	4/263 (1.5)	4/261 (1.5)	3/258 (1.2)
QTcF Interval				
High: >500 msec only	0/264 (0.0)	0/262 (0.0)	2/261 (0.8)	1/258 (0.4)
High: Increase ≥ 60 msec only	2/264 (0.8)	2/262 (0.8)	0/261 (0.0)	0/258 (0.0)
High: >500 and Increase ≥ 60	0/264 (0.0)	0/262 (0.0)	2/261 (0.8)	2/258 (0.8)
High: >500, Increase ≥ 60 msec or both	2/264 (0.8)	2/262 (0.8)	4/261 (1.5)	3/258 (1.2)
Heart Rate				
Low: < 50 bpm only	4/264 (1.5)	3/260 (1.2)	4/261 (1.5)	3/255 (1.2)
Low: Decrease ≥ 15 only	17/264 (6.4)	17/260 (6.5)	9/261 (3.4)	9/255 (3.5)
Low: < 50, Decrease ≥ 15 bpm or both	21/264 (8.0)	20/260 (7.7)	13/261 (5.0)	12/255 (4.7)
High: > 100 bpm and Increase ≥ 15	1/264 (0.4)	1/260 (0.4)	5/261 (1.9)	5/255 (2.0)
High: > 100 and Increase ≥ 15 bpm or > 120 and Increase ≥ 15 bpm	1/264 (0.4)	1/260 (0.4)	5/261 (1.9)	5/255 (2.0)

n = total patients who met PCS criteria at any point post Baseline.

N = total patients who had a ECG recorded after Baseline

N at BL = normal at Baseline, the number of patients who met PCS criteria for ECG at any time point after Baseline, and whose Baseline ECG was normal

PCS = potentially clinically significant.

* Patient 206-3692 had incorrect PR interval value of 0.750 seconds reported at end of study visit. The corrected value per the investigator is 0.170 seconds. The incorrect value was identified post-database lock, and thus the analysis reflects this incorrect value. The PCS outcomes for PR Interval for the trospium group reflect this incorrect data point.

6.0 Safety Conclusions:

- The AE's reported in this study are generally consistent with drugs of this class that are used to treat OAB.
- Nervous system events were rarely reported.
- Cardiac and ECG-related events were rarely reported. Excepting increased pulse rate (seen in 2 subjects in each treatment group), there were no cardiac-related events seen in more than one Sanctura XR treated subject.
- There were no deaths in either treatment group.
- There were no SAE's judged possibly related to study drug.
- The incidence of discontinuation due to constipation and dry mouth were 0.4 % and 1.0 %, and 0 % and 0.7 % for the placebo and trospium groups respectively.
- The overall incidence of TEAE's resulting in temporary interruption of study medication was similar between treatments groups. Two subjects (0.7%) were interrupted for dry mouth in the trospium group, while no placebo subjects were interrupted for constipation.
- The changes from baseline to endpoint were similar between groups for all laboratory parameters.
- Physical examinations were unremarkable, and changes in vital signs from baseline to endpoint were as expected, with a slight increase in the pulse rate seen in the trospium group, consistent with that noted in the Phase-3 trials of trospium 20 mg BID.
- Changes from baseline to endpoint for ECG's were comparable between groups, with no clinically meaningful differences among groups.

6.1 Overall Conclusions

- Sanctura XR demonstrated a statistically significant ($p = 0.0009$) improvement (ie, decrease) in average number of daily toilet voids at Week 12 when compared with placebo. Patients treated with Sanctura XR experienced an average reduction from 12.8 voids per day at baseline to 10.3 toilet voids per day at Week 12.
- Sanctura XR demonstrated a statistically significant ($p < 0.0001$) improvement (ie, decrease) in average number of UUI episodes per day at Week 12 compared with placebo. Patients treated with Sanctura XR experienced an average reduction from over 4 UUIs per day at baseline to less than 2 UUIs per day at Week 12.

Sanctura XR was well tolerated in this 12-week double-blind study. Compliance with study treatment and the completion rate of patients randomized was very good, and adverse events reported in this study were generally consistent with those events reported in other published studies of antimuscarinic compounds used to treat OAB. While constipation dry mouth were the events reported with the highest incidence, the actual reported incidence for these events was lower than that had been observed in studies of trospium chloride 20 mg BID.

There were no deaths and no treatment related serious adverse events in this study. Sanctura XR was found to be well-tolerated, to have an acceptable safety profile, and to provide clinically and statistically significantly greater improvements in OAB symptoms when compared to placebo.

This well-powered study of 564 OAB patients provides evidence that Sanctura XR has a comparable efficacy profile to that of the trospium chloride 20 mg BID formulation, and in many respects (specifically in terms of the incidence of TEAEs) may be superior to the 20 mg BID formulation for use in the treatment of patients with OAB.

A summary of key efficacy outcomes and TEAE incidence rates comparing Sanctura XR and the 20 mg BID formulations are seen in Tables 50 and 51.

Table 50. Efficacy of Trospium 20 mg (pooled data) Versus Sanctura XR, (SE): ITT:LOCF

Efficacy endpoint	Week	Trospium Chloride 20 mg BID	Trospium Chloride 60 mg XR Once- Daily
Number of daily toilet voids		N = 576	N = 267
Baseline	0	12.84 (0.11)	12.84 (0.18)
Change from Baseline	1	-1.32 (0.09)	-1.41 (0.16)
	4	-2.28 (0.11)	-2.25 (0.18)
	12	-2.53 (0.12)	-2.54 (0.19)
Number of daily UUI episodes		N = 576	N = 267
Baseline	0	3.86 (0.12)	4.02 (0.18)
Change from Baseline	1	-1.52 (0.09)	-1.70 (0.15)
	4	-2.09 (0.10)	-2.25 (0.16)
	12	-2.26 (0.11)	-2.35 (0.18)
Urgency severity score associated with toilet voids		N = 576	N = 267
Baseline	0	1.77 (0.02)	1.82 (0.03)
Change from Baseline	1	-0.10 (0.02)	-0.16 (0.03)
	4	-0.18 (0.02)	-0.28 (0.03)
	12	-0.21 (0.02)	-0.28 (0.03)
Volume voided (mL) per toilet void/day		N = 567	N = 266
Baseline	0	154.94 (1.99)	149.61 (2.94)
Change from Baseline	1	25.10 (1.84)	24.08 (2.35)
	4	35.34 (2.26)	29.29 (2.97)
	12	34.04 (2.34)	31.53 (3.39)
ITT=Intent to Treat, LOCF=Last Observation Carried Forward, SE=Standard Error			

Table 51. Trospium 20 mg BID Versus Sanctura XR, Possibly Related TEAE Incidence Rates

System Organ Class Preferred Term	Trospium Chloride 20 mg BID*		Trospium Chloride 60 mg XR Once-Daily	
	Placebo N = 590	Trospium N = 591	Placebo N = 284	Trospium N = 280
Gastrointestinal disorders				
Dry mouth	34 (5.8)	119 (20.1)	13 (4.6)	36 (12.9)
Constipation	27 (4.6)	57 (9.6)	5 (1.8)	21 (7.5)
Abdominal Pain Upper	7 (1.2)	9 (1.5)	1 (0.4)	4 (1.4)
Constipation Aggravated	5 (0.8)	8 (1.4)	0 (0.0)	4 (1.4)
Dyspepsia	2 (0.3)	7 (1.2)	1 (0.4)	1 (0.4)
Flatulence	5 (0.8)	7 (1.2)	1 (0.4)	7 (2.5)
Nervous system disorders				
Headache	12 (2.0)	25 (4.2)	6 (2.1)	5 (1.8)
General disorders				
Fatigue	8 (1.4)	11 (1.9)	1 (0.4)	0 (0.0)
Renal and urinary disorders				
Urinary Retention	2 (0.3)	7 (1.2)	1 (0.4)	1 (0.4)
Eye disorders				
Dry Eye	2 (0.3)	7 (1.2)	0 (0.0)	5 (1.8)

C. "120 Day Safety Update"

Background:

This "120 Day Safety Update Report" presents exposure and adverse event (AE) data from 769 patients with overactive bladder (OAB) treated with Sanctura XR for at least 6 months (≥ 24 weeks). In addition, 238 of these patients have at least 12 months (≥ 48 weeks) of treatment. These data were collected during the ongoing Open-Label phases of Studies IP631-018 and IP631-022 and include the data in the clinical database as of December 15, 2006.

Because there were no meaningful operational differences between the studies, a single description is provided here for both studies.

Table 1 provides a summary of the duration of exposure to date for subjects in the ongoing Open-Label phases for these 2 clinical studies.

Table 1: Duration of Exposure to Sanctura XR – All Patients Randomized (Studies IP631-018 and IP631-022 Combined)

	Placebo - Sanctura XR	Sanctura XR – Sanctura XR	Total
Number of Patients Randomized in Double-Blind Phase	587	578	1165
Number of Patients Enrolled in Open-Label Phase	483	459	942
Number of Patients with Duration of Treatment Derived ^a	476	459	935
Number of Patients with Duration of Treatment Not Derived ^a	7	0	7
Duration of Treatment with Sanctura XR (days)			
N	476	459	935
Mean (SE)	204.9 (3.91)	301.9 (3.55)	252.6 (3.08)
Median (range) ^c	238.5 (2 to 332)	339 (88 to 457)	269 (2 to 457)
Number of Patients with at Least 6 Months Exposure to Sanctura XR	354	415	769
Number (%) ^b of Patients with at Least 12 Months Exposure to Sanctura XR	0 ^d	238 (51.9)	238 (25.5)
Number (%) ^b of Patients with Exposure of:			
≥ 1 day to < 1 month (< 4 weeks)	26 (5.5)	0 (0.0)	26 (2.8)
≥ 1 month to < 3 months (≥ 4 weeks to < 12 weeks)	46 (9.7)	0 (0.0)	46 (4.9)
≥ 3 months to < 6 months (≥ 12 weeks to < 24 weeks)	50 (10.5)	44 (9.6)	94 (10.1)
≥ 6 months to < 12 months (≥ 24 weeks to < 48 weeks)	354 (74.4)	177 (38.6)	531 (56.8)
≥ 12 months (≥ 48 weeks)	0 ^d	238 (51.9)	238 (25.5)

^a Some Placebo to Sanctura XR patients did not have a valid date of first dose of Open-Label study medication in the clinical database as of the date of this long-term safety summary, and thus a duration of exposure to Sanctura XR was not derived for those patients.

^b Percentages based on number of patients with a non-missing duration of exposure.

^c Because the data in this summary are not yet completely queried or audited (both studies are still ongoing), the exposure for a few patients is currently being reported as over 1 year. Once data processing is completed for the studies, the exposure values reported by the investigators for these patients may change.

^d The Open-Label phases of the studies were up to 9 months, thus no Placebo to Sanctura XR patients have 12-month data.

Duration of treatment is defined as days from first dose of Open-Label medication for Placebo to Sanctura XR group, and first dose of Double-Blind medication for Sanctura XR to Sanctura XR group, to the exposure end date.

The exposure end date is defined as the Open-Label last dose date. If the subject completed or discontinued the Open-Label phase and the Open-Label last dose date is missing, then the Open-Label end of study date from the End of Study CRF is used. Otherwise, it is assumed that the subject is still enrolled in the Open-Label phase, thus the date the data was extracted from the clinical database is used (December 15, 2006).

The demographic characteristics of the subjects included in this safety update report are summarized in Table 2.

Table 2: Demographic and Baseline Characteristics – Patients with at Least 6 Months Exposure to Sanctura XR (Studies IP631-018 and IP631-022 Combined)

Characteristic	Placebo - Sanctura XR (N=354)	Sanctura XR - Sanctura XR (N=415)
Age (in years)		
Mean ± SE	58.8 ± 0.58	60.6 ± 0.61
Median (range)	59 (27 – 83)	61 (21 – 88)
Age Categories, n (%)		
<65 years	244 (68.9)	250 (60.2)
65 to <75 years	88 (24.9)	105 (25.3)
≥75 years	22 (6.2)	60 (14.5)
Gender, n (%)		
Female	308 (87.0)	349 (84.1)
Male	46 (13.0)	66 (15.9)
Race, n (%)		
White	301 (85.0)	369 (88.9)
Black	36 (10.2)	29 (7.0)
Hispanic	8 (2.3)	11 (2.7)
Asian	5 (1.4)	3 (0.7)
Other	4 (1.1)	3 (0.7)
Height ^a (in cm)		
Mean ± SE	164.2 ± 0.54	164.9 ± 0.42
Weight ^a (in kg)		
Mean ± SE	87.5 ± 1.15	86.9 ± 1.09
Prior anticholinergic use for OAB, N (%)		
Naïve	160 (45.2)	190 (45.8)
Non-naïve	194 (54.8)	225 (54.2)

^a A few patients did not have values reported for some parameters.
SE = standard error. OAB = overactive bladder.

Adverse Events

Events reported here are only new onset TEAEs from the Open-Label portion of the studies. “Carry-over” AEs that first occurred in the Double-Blind phase are not reported here as those events were already reported in the NDA submission.

Table 3 presents a summary of subjects with at least 6 months of exposure to Sanctura XR, with new onset Open-Label TEAE’s regardless of relationship to the study drug occurring in at least 5 subjects during the Open-Label phase by original randomization treatment group.

Table 3: Incidence of Open-Label TEAEs Regardless of Relationship Reported in at Least 5 Patients by Preferred Term – Patients with at Least 6 Months Exposure to Sanctura XR (Studies IP631-018 and IP631-022 Combined)

MedDRA Preferred term	Number of patients (%)		
	Placebo - Sanctura XR N = 354	Sanctura XR - Sanctura XR N = 415	Total N = 769
Total patients with at least 1 open-label TEAE	169 (47.7)	191 (46.0)	360 (46.8)
Urinary tract infection	20 (5.6)	22 (5.3)	42 (5.5)
Constipation	22 (6.2)	18 (4.3)	40 (5.2)
Dry mouth	24 (6.8)	11 (2.7)	35 (4.6)
Upper respiratory tract infection	11 (3.1)	8 (1.9)	19 (2.5)
Hypertension	9 (2.5)	10 (2.4)	19 (2.5)
Sinusitis	6 (1.7)	12 (2.9)	18 (2.3)
Arthralgia	8 (2.3)	5 (1.2)	13 (1.7)
Bronchitis	2 (0.6)	9 (2.2)	11 (1.4)
Nausea	5 (1.4)	5 (1.2)	10 (1.3)
Diarrhea	4 (1.1)	5 (1.2)	9 (1.2)
Fatigue	2 (0.6)	7 (1.7)	9 (1.2)
Nasopharyngitis	6 (1.7)	3 (0.7)	9 (1.2)
Headache	5 (1.4)	4 (1.0)	9 (1.2)
Edema peripheral	6 (1.7)	2 (0.5)	8 (1.0)
Back Pain	2 (0.6)	5 (1.2)	7 (0.9)
Dysuria	3 (0.8)	4 (1.0)	7 (0.9)
Rash	3 (0.8)	4 (1.0)	7 (0.9)
Blood pressure increased	4 (1.1)	2 (0.5)	6 (0.8)
Gastroesophageal reflux disease	2 (0.6)	4 (1.0)	6 (0.8)
Influenza	3 (0.8)	3 (0.7)	6 (0.8)
Dizziness	2 (0.6)	4 (1.0)	6 (0.8)
Depression	2 (0.6)	4 (1.0)	6 (0.8)
Nephrolithiasis	4 (1.1)	2 (0.5)	6 (0.8)
Constipation aggravated	3 (0.8)	2 (0.5)	5 (0.7)
Urinary retention	1 (0.3)	4 (1.0)	5 (0.7)
Migraine	3 (0.8)	2 (0.5)	5 (0.7)
Tachycardia	2 (0.6)	3 (0.7)	5 (0.7)

Table 4 presents a summary, in patients with at least 12 months of exposure to Sanctura XR, of new onset TEAEs regardless of relationship to study drug occurring in at least 2 patients during the Open-Label phase by original randomization treatment group,

Table 4: Incidence of Open-Label TEAEs Regardless of Relationship Reported in at Least 2 Patients by Preferred Term – Sanctura XR to Sanctura XR Patients with 12 Months Exposure to Sanctura XR (Studies IP631-018 and IP631-022 Combined)

MedDRA Preferred term	Number of patients (%)
	Sanctura XR to Sanctura XR N = 238
Total patients with at least 1 Open-Label TEAE	112 (47.1)
Urinary tract infection	15 (6.3)
Sinusitis	10 (4.2)
Constipation	7 (2.9)
Dry mouth	6 (2.5)
Hypertension	6 (2.5)
Bronchitis	6 (2.5)
Gastroesophageal reflux disease	4 (1.7)
Upper respiratory tract infection	4 (1.7)
Contusion	4 (1.7)
Arthralgia	4 (1.7)
Tachycardia	3 (1.3)
Vomiting	3 (1.3)
Fatigue	3 (1.3)
Gastroenteritis Viral	3 (1.3)
Influenza	3 (1.3)
Nasopharyngitis	3 (1.3)
Fall	3 (1.3)
Back Pain	3 (1.3)
Rash	3 (1.3)
Abdominal pain upper	2 (0.8)

Table 4 (continued)

MedDRA Preferred term	Number of patients (%)
	Sanctura XR to Sanctura XR N = 138
Dyspepsia	2 (0.8)
Gastritis	2 (0.8)
Nausea	2 (0.8)
Edema peripheral	2 (0.8)
Cystitis	2 (0.8)
Pneumonia	2 (0.8)
Staphylococcal infection	2 (0.8)
Back injury	2 (0.8)
Joint sprain	2 (0.8)
Meniscus lesion	2 (0.8)
Skin laceration	2 (0.8)
Weight decreased	2 (0.8)
Hypercholesterolemia	2 (0.8)
Dizziness	2 (0.8)
Headache	2 (0.8)
Migraine	2 (0.8)
Asthma	2 (0.8)

TEAE = treatment-emergent adverse event

The incidence of new-onset, Open-Label TEAEs, in subjects with at least 6 months of exposure to Sanctura XR, judged by the investigator as being at least possibly related to study treatment and occurring in at least 2 subjects is provided in Table 5.

Table 5: Incidence of At Least Possibly Related Open-Label TEAEs Reported in at Least 2 Patients by Preferred Term – Patients with at Least 6 Months Exposure to Sanctura XR (Studies IP631-018 and IP631-022 Combined)

MedDRA Preferred term	Number of patients (%)		
	Placebo - Sanctura XR N = 354	Sanctura XR - Sanctura XR N = 415	Total N = 769
Total patients with at least 1 at least possibly related Open-Label TEAE	61 (17.2)	50 (12.0)	111 (14.4)
Constipation	19 (5.4)	16 (3.9)	35 (4.6)
Dry mouth	23 (6.5)	11 (2.7)	34 (4.4)
Headache	3 (0.8)	2 (0.5)	5 (0.7)
Urinary retention	1 (0.3)	4 (1.0)	5 (0.7)
Constipation aggravated	3 (0.8)	2 (0.5)	5 (0.7)
Urinary tract infection	3 (0.8)	0 (0.0)	3 (0.4)
Fatigue	2 (0.6)	2 (0.5)	4 (0.5)
Dyspepsia	1 (0.3)	2 (0.5)	3 (0.4)
Dysuria	1 (0.3)	2 (0.5)	3 (0.4)
Blood pressure increased	1 (0.3)	2 (0.5)	3 (0.4)
Dizziness	0 (0.0)	3 (0.7)	3 (0.4)
Dysgeusia	2 (0.6)	1 (0.2)	3 (0.4)
Dry eye	1 (0.3)	1 (0.2)	2 (0.3)
Nausea	2 (0.6)	0 (0.0)	2 (0.3)
Diarrhea	1 (0.3)	1 (0.2)	2 (0.3)
Abdominal pain	0 (0.0)	2 (0.5)	2 (0.3)
Asthma	2 (0.6)	0 (0.0)	2 (0.3)

The incidence of new-onset, Open-Label TEAEs, in subjects with at least 12 months of exposure to Sanctura XR, judged by the investigator as being at least possibly related to study treatment and occurring in at least 2 subjects is provided in Table 6.

Table 6: Incidence of At Least Possibly Related Open-Label TEAEs Reported in at Least 2 Patients by Preferred Term – Sanctura XR to Sanctura XR Patients with 12 Months Exposure to Sanctura XR (Studies IP631-018 and IP631-022)

MedDRA Preferred term	Number of patients (%)
	Sanctura XR to Sanctura XR (N = 238)
Total patients with at least 1 at least possibly related Open-Label TEAE	21 (8.8)
Dry mouth	6 (2.5)
Constipation	5 (2.1)
Dizziness	2 (0.8)
Headache	2 (0.8)

Table 7 presents the incidence of new-onset, Open-Label TEAEs occurring in at least 2.0% of all subjects with at least 6 months of exposure to Sanctura XR, by < 65 year and ≥ 65 year age subgroups, while **Table 8** presents the incidence of select at least possibly related TEAEs by these age subgroups.

Table 7: Incidence of Open-Label TEAEs (Regardless of Relationship to Study Drug) Occurring in at Least 2.0% of All Patients by Preferred Term and Age Subgroups (<65 and ≥ 65 years) – Patients With At Least 6 Months Exposure to Sanctura XR (Studies IP631-018 and IP631-022 Combined)

MedDRA Preferred term	Number of patients (%)			
	Placebo - Sanctura XR N = 354		Sanctura XR - Sanctura XR N = 415	
	< 65 years (N=244)	≥ 65 years (N=110)	< 65 years (N=250)	≥ 65 years (N=165)
Total patients with at least 1 Open-Label TEAE	117 (48.0)	52 (47.3)	116 (46.4)	75 (45.5)
Urinary tract infection	16 (6.6)	4 (3.6)	7 (2.8)	15 (9.1)
Constipation	14 (5.7)	8 (7.3)	10 (4.0)	8 (4.8)
Dry mouth	16 (6.6)	8 (7.3)	7 (2.8)	4 (2.4)
Upper respiratory tract infection	8 (3.3)	3 (2.7)	6 (2.4)	2 (1.2)
Hypertension	9 (3.7)	0 (0.0)	5 (2.0)	5 (3.0)
Sinusitis	6 (2.5)	0 (0.0)	7 (2.8)	5 (3.0)

Table 8: Incidence of Select At Least Possibly Related Open-Label TEAEs by Preferred Term and Age Subgroups (<65 and ≥ 65 years) – Patients With At Least 6 Months Exposure to Sanctura XR (Studies IP631-018 and IP631-022 Combined)

MedDRA Preferred term	Number of patients (%)			
	Placebo - Sanctura XR N = 354		Sanctura XR - Sanctura XR N = 415	
	< 65 years (N=244)	≥ 65 years (N=110)	< 65 years (N=250)	≥ 65 years (N=165)
Total patients with at least 1 at least possibly related Open-Label TEAE	40 (16.4)	21 (19.1)	30 (12.0)	20 (12.1)
Constipation	12 (4.9)	7 (6.4)	9 (3.6)	7 (4.2)
Dry mouth	16 (6.1)	8 (7.3)	7 (2.8)	4 (2.4)
Urinary retention	1 (0.4)	0 (0.0)	2 (0.8)	2 (1.2)
Urinary tract infection	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	2 (0.8)	1 (0.9)	2 (0.8)	0 (0.0)

Adverse Events of Interest

New-onset, Open-Label TEAEs of interest were reviewed for all subjects with at least 6 months or more of exposure. As described in the original study protocols, events of interest were to be given special attention. These events of interest were defined as:

- anticholinergic events such as dry mouth, constipation, dry eyes, residual urine volume (urinary retention), and rash.
- nervous system disorders such as headache and dizziness.
- cardiac-related events such as chest pain of a cardiac nature, angina pectoris, and myocardial infarction.

In addition, the following events were given special attention and are thus included here: gut motility events (including constipation, aggravated constipation, abdominal distension, abdominal discomfort, abdominal pain, lower abdominal pain, fecaloma, and feces hard).

- UTI and urinary retention.

The anticholinergic events that occurred with the highest incidence during the Open-Label phase included constipation and dry mouth. All constipation events were judged as mild or moderate in severity. There was one report of a subject with severe dry mouth, while the remaining reports of dry mouth were judged to be either mild or moderate in severity. New onset of dry eye was reported for only 2 subjects during the Open-Label phase (both events were judged as mild and possibly related to study medication) and there were 7 new reports of rash (1 of which was judged as possibly related to study medication). Urinary retention was reported in 5 patients, and each of these events was reported to be at least possibly related to study medication. Two of the urinary retention events were judged to be severe by the investigator.

New onset of headache and dizziness were each reported in fewer than 1% of patients, with approximately half of these events judged to be at least possibly related to study treatment.

There were no reports of severe headache or dizziness.

Cardiac-related events were rare. Single reports of first degree atrioventricular block, bradycardia, tachycardia, and left bundle branch block were the only cardiac-related events

reported that were judged to be at least possibly related to study medication.

Gut motility events were the most common events of interest that started during Open-Label phase, with constipation being the most frequent. Other gut motility events (eg, abdominal discomfort, abdominal distension, and abdominal pain) were rarely reported. The majority of constipation events were judged to be mild in severity and at least possibly related to study treatment, and no constipation event was judged to be severe. There were 5 reports of aggravated constipation (from subjects who had a medical history of constipation prior to entry into the study), each of which was judged to be at

least possibly related to study treatment. One of these reports of aggravated constipation was judged to be severe.

Only 3 subjects had one or more at least possibly related UTIs, and all other subjects (39 of 42 subjects) with UTIs had the causal relationship assessed as remote or definitely not related to the study medication (causal relation was judged by the investigator). There was 1 severe UTI reported, while the remaining reports were judged to be mild or moderate in severity. At the Double-Blind Day-84, End-of-Study visit, Subject 036-6114 (originally randomized to the Sanctura XR treatment group in the double-blind phase) reported to the investigator that she was pregnant. Because of the pregnancy, the subject was not continued into the Open-Label phase; however, we report the outcome of the pregnancy here. The subject had reported taking birth control since 2003 (Lovia 1/50 daily [QD]). The subject found out about the pregnancy the week prior to the Day-84 visit (she was 6 weeks pregnant at the time of the End-of-Study visit). The investigator followed the subject through to the end of her pregnancy, and reported that the subject gave birth, without complications, to a healthy baby.

SAE's

A total of 35 (4.6%) subjects experienced at least 1 new-onset, Open-Label SAE. None of these SAEs was judged to be at least possibly related to study medication by the investigators. The SAEs reported in 2 or more subjects were: noncardiac chest pain (3, 0.4%), cerebrovascular accident (2, 0.3%), lumbar spinal stenosis (2, 0.3%), nephrolithiasis (2, 0.3%) and pulmonary embolism (2, 0.3%). No other SAE was reported in more than 1 subject. There were 2 serious gastrointestinal system events, each reported in 1 subject: ulcerative colitis and gastroesophageal reflux disease. There were no serious constipation or other gut motility events reported. There was no serious urinary retention events reported, while there was 1 serious UTI event reported.

AE's Resulting in Discontinuation from Study

A total of 22 (2.9%) subjects experienced an Open-Label TEAE that resulted in premature discontinuation from the Open-Label phase, and most of these TEAEs were judged to be at least possibly related to study medication by the investigators. Only 3 TEAEs resulted in premature discontinuation in more than one subject: dry mouth (4, 0.5%), constipation (2, 0.3%) and dizziness (2, 0.3%). There was 1 subject who discontinued due to aggravated constipation and 1 subject who discontinued due to abdominal pain.

Deaths

Three subjects died during the open-label treatment phase. Two subjects died from causes judged by the investigator to be unrelated to the study medication, while the cause of the third death is unconfirmed at this time (the subject apparently died from

complications of preexisting cancer, and on-going collection of data regarding the death is underway). Brief narratives for these 3 subjects are provided below:

Subject 261-3355 was a 48-year old (at screening) white female who had been randomized to active study medication in the Double-Blind study phase. She was first treated with Sanctura XR on [redacted]. Her past medical history is significant for seasonal allergies, lower back and bilateral knee pain, tension headaches and depression. She was taking Flonase and Allegra PRN since 2000 for her allergies and Desogen since 2003 for birth control. On [redacted] (193 days following her first dose of study medication), the subject experienced a pulmonary embolism. An autopsy was performed and the cause of death was pulmonary thromboembolism. The event was judged by the investigator to be definitely not related to study medication.

Subject 035-6400 was a 54-year old (at screening) white female who had been randomized to active study medication in the Double-Blind study phase. She was first treated with Sanctura XR on [redacted]. Her past medical history includes hypothyroidism since 1988 treated with daily synthroid replacement and post-menopause since 2000. She had been taking Triest and progesterone gel since 2000. The subject had a history of abnormal stress tests. On [redacted] (143 days following her first dose of study medication), the subject experienced a series of events, including a left internal carotid artery occlusion, hypertension, an acute cerebral infarct (a stroke in the middle cerebral artery territory), and a brain stem herniation. The subject died the next day on [redacted] because of the herniation. All events were judged by the investigator to be definitely not related to study medication.

Subject 241-3688 was an 84-year old (at randomization) white female who had been randomized to placebo in the Double-Blind study phase. She was first treated with Sanctura XR on [redacted]. The subject had a medical history of colon cancer, hypertension, seasonal allergies, transient ischemic attack in 2005, hysterectomy, ovarian cyst, bladder sling, arthritis, and hypothyroidism. She had been taking aspirin, benicar, Protonix, synthroid, and fish oil. On [redacted] (167 days following her first dose of active study medication), the subject was diagnosed with metastatic gynecologic malignancy to the right chest peritoneum (malignant pleural effusion), presumed ovarian, for which she received chemotherapy. The event was considered resolved with sequelae and judged by the investigator to be definitely not related to study medication. On [redacted] (179 days following her first dose of active study medication), the subject experienced a pulmonary embolism, which was considered resolved with sequelae and judged by the investigator to be definitely not related to study medication. The subject withdrew from the study on November 30, 2006, citing that her chemotherapy would be very involved over the next several months, but only returned her study medication and was not seen for the early termination visit. A member of the site staff happened to notice in the local newspaper's obituary page that the subject had died on [redacted]. The study site obtained the certificate of death which indicated that the cause of death was metastatic cancer of unknown primary origin.

Summary

The data for this safety update comes from subjects who voluntarily participated in the Open-Label extension part of the two Phase 3 clinical studies, IP631-018 and IP631-022, which were reported in the original NDA 22-103. This summary presents exposure and adverse event data from 769 subjects with OAB who were treated with Sanctura XR for at least 6 months (≥ 24 weeks). In addition, 238 of these subjects had at least 12 months (≥ 48 weeks) of treatment with Sanctura XR. These data were collected during the ongoing Open-Label phases of Studies IP631-018 and IP631-022 and include the data in the clinical database as of December 15, 2006.

Regardless of causal relationship to study medication, at least one new-onset, Open-Label TEAE was reported in 360 of the 769 patients (46.8%) with at least 6 months of exposure to Sanctura XR. TEAEs were most commonly reported in the gastrointestinal system. Most events were judged by the investigators to be mild or moderate in severity. There were 111/769 (14.4%) patients who experienced 1 or more TEAE that was considered by the investigator as at least possibly-related to study medication, with constipation (4.6%), and dry mouth (4.4%) the most common of these events. The rates observed in this Open-Label phase were significantly lower than the rates observed during the Double-Blind phase (eg, during the Double-Blind phase, the at least possibly-related TEAE incidence rates were 8.5% for constipation and 10.7% for dry mouth). This disparity occurs in part because the Sanctura XR to Sanctura XR subjects with such TEAEs would have already reported the events during the Double-Blind phase.

There was no increase in the incidence of gut-motility-related, antimuscarinic-type events in the subgroup of subjects with at least 12 months of exposure to Sanctura XR when compared to subjects with at least 6 months of exposure.

TEAEs were assessed by subgroups to discern whether there was an association between demographic characteristics and the incidence of specific events reported. There were no clinically meaningful differences between the treatment groups in the incidence of any new-onset, Open-Label TEAEs by subgroups. Of note, there was no difference noted between age subgroups in terms of overall TEAE incidence, and further, for the most commonly reported TEAEs (eg, dry mouth, constipation, urinary tract infection), incidence rates did not increase from the younger subgroup to the older subgroup. When TEAEs judged to be at least possibly related by the investigator were reviewed for age subgroup differences, the incidence rates of these events were similar between the age subgroups.

A total of 35/769 (4.6%) subjects experienced at least one SAE during the Open-Label phase. None of these SAEs were judged to be at least possibly related to study medication by the investigators. Five SAEs were reported in more than one subject: non-cardiac chest pain (3, 0.4%), cerebrovascular accident (2, 0.3%), lumbar spinal stenosis (2, 0.3%), nephrolithiasis (2, 0.3%) and pulmonary embolism (2, 0.3%). No other SAE was reported in more than 1 subject. There were 3 deaths reported, however, no deaths were judged by the investigators to be related to drug treatment. A total of 22 (2.9%) patients experienced an Open-Label TEAE that resulted in premature discontinuation from the Open-Label phase, and most of these TEAEs were judged to be at least possibly-related to study medication by the investigators. Only 3

TEAEs resulted in premature discontinuation in more than one patient: dry mouth, constipation and dizziness.

Conclusions

There were no un-expected events observed during the Open-Label treatment period, and there were no serious adverse events or deaths considered related to treatment with Sanctura XR. The incidence and severity of gut-motility events during up to 12 months of treatment was low. The safety data compiled for this 120 Day Safety Update Report are consistent with those reported during the original NDA filing of the Double-Blind data, and **support the conclusion that Sanctura XR is generally well-tolerated and safe for the target population.**

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/s/

Harry Handelsman
7/17/2007 03:45:42 PM
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7/17/2007 03:55:52 PM
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NDA 22-103

Medical Officer's Memorandum: NDA Filing Review

Date Submitted: October 13, 2006
Date Received: October 18, 2006
Draft memo complete: November 20, 2006
Revisions complete: November 30, 2006

Drug Product: Sanctura XR (trospium chloride extended release capsules)
Dose: 60mg once daily
Sponsor: Indevus Pharmaceuticals, Inc.
Indication: Overactive Bladder

I. Executive Summary

Objective:

The purpose of this memo is to fulfill the regulatory requirement that a NDA be reviewed to determine its suitability for filing under 21 CFR 314. This memorandum also serves to document potential review issues identified during the Clinical filing review period.

Conclusion:

A Clinical filing review of the submitted safety and efficacy information, and dosing recommendations for Sanctura XR was conducted. Review of the clinical sections of the NDA submission failed to identify any deficiencies that would constitute the basis for a Refuse-to File action. In the opinion of this reviewer, the information and data in the submitted application is adequate to permit a substantive clinical review. One potential review issues were identified, as follows:

1. The incidence and severity of reported adverse events of constipation will be a review issue.

This single potential review issue should be conveyed to Sponsor in the 74-Day letter.

II. Administrative Filing Review

Drug Product:

Trospium chloride (trospium) is an ammonium derivative of atropine. It has predominant peripheral antimuscarinic activity that antagonizes the effect of acetylcholine. It also acts as a parasympatholytic, which in the urogenital tract enables detrusor relaxation and subsequent inhibition of bladder evacuation, leading to enhanced bladder compliance with increased bladder capacity and urinary control.

Trospium was first marketed in Germany in 1967 as a spasmolytic agent and received pan-European approval in the 1990's for specific therapeutic indications, including symptoms of overactive bladder (OAB). FDA approval of trospium 20 mg BID, for treatment of OAB associated with symptoms of

urinary incontinence, urgency and frequency, occurred in May, 2004. This current submission proposes a once daily (morning) dosage of trospium 60 mg in an extended release capsule (Sanctura XR) for the same indication.

Basic Contents of the NDA:

This NDA submission includes data from three Phase 1 pharmacokinetic and tolerability studies (82 subjects), a single Phase 2 study (148 subjects), and two Phase 3 studies (1165 subjects).

Review Method:

This review is based on criteria proposed in FDA's guidance for filing, reflecting FDA's interpretation of 21 CFR 314.101 (d)(3), specifically:

- Is there omission or incomplete submission of a required section of the NDA under 21 CFR 314.50?
- Is there failure to include evidence of effectiveness compatible with statutes and regulations?
- Is there omission of critical data, information or analyses necessary for evaluation of safety and effectiveness, or failure to provide adequate directions for product use?

Filing Review Results:

1. Does the submission have omissions or incomplete presentations of required sections as listed in Table 1?

Answer: No. The NDA contains the critical sections in sufficient detail to conduct an adequate Clinical review.

Table 1. Checklist for Critical Sections of the NDA

<u>Required Sections (21 CFR 314.50)</u>	<u>Archive Copy Location</u>
The proposed text of the labeling. (c)(2)(i)	m1\114-label\1141-draft-label\proposed.doc
A summary of the clinical data. (c)(2)(viii)	m5\53-clin-stud-rep\535-rep-effic-safety-stud\5353-rep-analys-data-more-one-stud\ip631-018-022.pdf
Technical sections. (d)	m2toc.pdf
Controlled Clinical Studies. (including summaries of efficacy (d)(5)(ii), safety (d)(5)(vi), benefits/risks (d)(5)(viii)).	m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\ip631-018.pdf m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr\ip631-022.pdf
Case report forms and tabulations. (f)	(forms) m5\53-clin-stud-rep\537-crf-ipl\crftoc.pdf (tabs) m5\datasets\datatoc.pdf
Financial certification and disclosure. (k)	m1\13-admin-info\financial-cert.pdf

2. Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations?

Answer: No. The sponsor provided data from two (2), large, multi-center (129 U.S. sites), randomized, double-blind, placebo-controlled studies of the safety and efficacy of Sanctura XR once daily, for 12 weeks followed by an 9-month open-label treatment phase in subjects with OAB. The studies appear to be adequate and well controlled. The primary efficacy variables (based on diary reports) were:

- The change in average number of toilet voids per day.
- The change in urinary urge incontinence (UUI) episodes per day.

Secondary endpoints included: average urine volume voided per micturition and health-related quality of life instruments, such as the King's Health Questionnaire and the OAB-q.

The Sponsor purports that changes-from-baseline in both primary endpoints were statistically significant as compared to placebo. The internal consistency of the secondary efficacy provides support for the findings from the primary efficacy analyses.

3. Does the NDA omit critical data, information or analyses needed to evaluate safety and effectiveness or fail to provide adequate directions for product use?

Answer: No. The Phase 3 studies included a total of 1165 subjects. This is sufficient to assess safety for Sanctura XR for the treatment of overactive bladder. The randomized patients were predominately female (approx. 85 %) with median age of approximately 58-59 years, range 21-90. The treatment groups were well matched for demographic and baseline characteristics and were representative of the patient population commonly diagnosed with OAB. At of the time of submission of this original NDA, approximately 417 patients had received at least 6 months of Sanctura XR.

III. Summary of the Controlled Phase 3 Studies

Studies IP631-018 and IP631-022 were Phase-3, double-blind, multi-center, randomized, placebo-controlled studies of safety and efficacy of Sanctura XR versus placebo, once daily, for 12 weeks. Patients were offered the opportunity to continue treatment in a 9-month, open-label, extension phase. All sites were in the United States. It is notable that Study -018 was initially planned to include up to 10 European sites, however, no European site enrolled patients

Study Objectives

To evaluate the effects of once daily dosing of trospium chloride extended release capsules (60 mg) compared to placebo, on urinary frequency, urge incontinence episode frequency, and other symptoms associated with OAB, over a 12-week period.

Study Design and Procedures.

The two studies were identical in design. Patients taking other OAB therapies were required to undergo a 7-day washout period prior to the Baseline 3-day urinary diary. Treatment-naïve patients began the study with the Baseline 3-day diary. Patients were randomized to drug or placebo on a 1:1 basis. All randomized patients continued in the double-blind treatment phase for a total duration of

12 weeks. Randomization was stratified by the mean baseline number of toilet voids per 24 hours to assure a fair distribution of disease severity within the 2 treatment groups. Patients were evaluated periodically during the 12-week period and were offered the opportunity to continue into an open-label phase of the trial for up to 9-months.

Demographics

Randomized patients were predominantly middle-aged, Caucasian, and females. There were no significant differences in the baseline characteristics in the two studies: Age ranged from 21-90, and more specifically: age <65 (60-68 %), age 65 to <75 (22- 26 %), age ≥75 (10-15 %). In terms of gender: females, 82-88 %, males, 12-18%. In terms of race: White 82-88 %, Black 6-10 %, Hispanic 2-5 %, Other 1-2 %. Finally, approximately 45-50% of all patients had previously taken medication for overactive bladder.

Efficacy Results

Study-018: A statistically significant ($p < 0.0001$) decrease in average number of toilet voids per day compared to placebo was observed at week 12. A statistically significant ($p = 0.0022$) decrease in average number of urge urinary incontinence (UUI) episodes per day was also observed at week 12. A summary of key results for these diary-based efficacy endpoints is shown in Table 2. A negative change (decrease from baseline) indicates improvement.

Table 2. Study-018

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Toilet voids		<i>N = 300</i>	<i>N = 292</i>	
Baseline	0	12.74	12.78	0.9564
Change from baseline	1	-1.24	-1.66	0.0092
	4	-1.58	-2.44	<0.0001
	12	-1.99	-2.81	<0.0001
UUI Episodes/Day		<i>N = 300</i>	<i>N = 292</i>	
Baseline	0	4.14	4.11	0.8144
Change from baseline	1	-1.24	-1.86	0.0003
	4	-1.75	-2.36	0.0051
	12	-1.93	-2.48	0.0022
UUI Episodes/Week		<i>N = 300</i>	<i>N = 292</i>	
Baseline	0	28.98	28.77	0.8144
Change from baseline	1	-8.66	-13.03	0.0003
	4	-12.24	-16.50	0.0054
	12	-13.49	-17.34	0.0024

Study-022: A statistically significant ($p = 0.0009$) decrease in average number of toilet voids per day compared to placebo was observed at week 12. A statistically significant decrease in average number of UUI episodes per day compared to placebo was also observed at week 12. A summary of key efficacy results for these diary-based efficacy endpoints is shown in Table 3. A negative change (decrease from baseline) indicates improvement.

Table 3. Study-022

Efficacy endpoint	Week	Placebo	Sanctura XR	p-value
Toilet voids		<i>N</i> = 276	<i>N</i> = 267	
Baseline	0	12.94	12.84	0.2201
Change from baseline	1	-1.15	-1.41	0.0759
	4	-1.71	-2.25	<0.0047
	12	-1.80	-2.54	<0.0009
UUI Episodes/Day		<i>N</i> = 276	<i>N</i> = 267	
Baseline	0	4.04	4.02	0.5401
Change from baseline	1	-1.04	-1.70	<0.0001
	4	-1.51	-2.25	<0.0001
	12	-1.62	-2.35	<0.0001
UUI Episodes/Week		<i>N</i> = 276	<i>N</i> = 267	
Baseline	0	28.31	28.15	0.5401
Change from baseline	1	-7.30	-11.89	<0.0001
	4	-10.58	-15.75	<0.0001
	12	-11.33	-16.43	<0.0001

Safety Results:

The safety results for Sanctura XR were derived from reports of clinical adverse events, and monitoring of clinical laboratories, ECGs, physical examinations and vital signs, in the clinical trials.

A total of 1165 patients were randomized into the 2 pivotal studies, and approximately 88 % completed the full, 12-week course. The findings from both studies were similar and consistent. One or more treatment emergent adverse events (TEAE's) were experienced by 27.2 % of study drug patients and 16.7 % of placebo patients. The incidence of TEAE's reported in at least 1 % of patients is shown in Table 4:

Table 4. Incidence of Treatment Emergent Adverse Events in the Phase 3 studies

MedDRA Preferred Term	Number of Patients (%)	
	Placebo	Sanctura XR
	<i>N</i> = 587	<i>N</i> = 578
Dry mouth	22 (3.7)	62 (10.2)
Constipation	9 (1.5)	49 (8.5)
Dry eye	1 (0.2)	9 (1.6)
Flatulence	3 (0.5)	9 (1.6)
Nausea	2 (0.3)	8 (1.4)
Abdominal pain	2 (0.3)	8 (1.4)
Dyspepsia	4 (0.7)	7 (1.2)
Urinary tract infection	5 (0.9)	7 (1.2)
Constipation aggravated	3 (0.5)	7 (1.2)
Abdominal distension	2 (0.3)	6 (1.0)
Nasal dryness	0 (0.0)	6 (1.0)

As demonstrated in Table 4, for both pivotal studies, the expected treatment-related adverse events (TEAEs) associated with this class of drugs was reported: dry mouth 9-13 % and constipation 7-9 %. No other treatment-related AE's were seen in >2 % of subjects. ECG changes from baseline were comparable between all treatment groups and no clinically meaningful differences were identified.

There were no deaths in either study. There were 10 (1.7 %) patients in the placebo group and 8 (1.4 %) in the Sanctura XR group that had at least 1 SAE, but none were judged by the investigator as being related to study medication.

The mean and median changes from baseline to endpoint for clinical laboratories, ECG parameters, and the vital sign assessments were small and not clinically meaningful.

Reviewer's Comment: The study design for the 2 pivotal studies was appropriate for both dose and indication. The enrolled patient population appears to mimic the general OAB population in both demographics and other characteristics such as symptoms and comorbidities. The reported clinical AE's are those expected for this class of drugs and were generally tolerated. The key efficacy analysis focused on change from Baseline to the Week 12 visit using both the intent-to-treat (last observation carried forward) data sets. The primary efficacy endpoints achieved statistical significance in demonstrating decreases in both primary endpoints: the number of toilet voids and UUI episodes. The clinical benefit of this demonstrated treatment effect will be further examined using responder analyses and results from secondary endpoints.

Other data related to safety will be derived from the ongoing 9-month open-label extension treatment phase of these studies. Data from patients with at least 6 months exposure was submitted with this original NDA and the clinical adverse events judged to be at least possibly related to study drug by the investigator are shown in Table 5.

Table 5. Incidence of Clinical Adverse Events in the Ongoing Open-Label Extension Study (at least 6 months of treatment received)

MedDRA Preferred Term	Number of Patients (%)	
	Placebo- Sanctura XR N= 222	Sanctura XR- Sanctura XR N= 417
Constipation	10 (4.5)	18 (4.3)
Dry mouth	10 (4.5)	9 (2.2)
Elevated blood pressure	1 (0.5)	3 (0.7)
Urinary retention	1 (0.5)	2 (0.5)
Dyspepsia	0 (0.0)	2 (0.5)
Fatigue	0 (0.0)	2 (0.5)
Dizziness	0 (0.0)	2 (0.5)
Dysuria	0 (0.0)	1 (0.2)
Asthma	2 (0.9)	0 (0.0)

Reviewer's Comment: As shown in Tables 4 and 5, the anticipated AE's, dry mouth and constipation, are the most frequently recorded events, ranging from 10.2% and 8.5%, respectively, in the initial studies to 4.4% and 3.0% in the preliminary data from the ongoing extension study. These numbers may suggest that some degree of tolerance to these particular AE's develops after longer term exposure to drug.

Other clinical studies submitted in this NDA included three, Phase-1, PK and tolerability studies. These were conducted as part of the early formulation- and dose-finding phase of this drug development program. They had the following objectives:

- To determine the pharmacokinetics of four different, once-daily formulations
- To compare the bioavailability of Sanctura XR in fasted, fed, or antacid treated subjects
- To characterize the steady-state PK and relative bioavailability of the 60 mg XR preparation compared with the 20 mg dose BID.

Finally, Study IP631-016 was a Phase-2 trial evaluating the effects of Sanctura XR given in the morning versus in the evening, and included blood sampling for PK assessments. In this study, the incidences of dry mouth and constipation were slightly higher in the evening-dosed patients, and a small but significant correlation of drug concentration and the incidence of dry mouth was seen following morning dosing.

IV. Recommended Regulatory Action

The NDA is considered fileable from a Clinical perspective. A single Clinical comment should be conveyed to Sponsor in the 74-Day Letter as follows:

"The incidence and severity of reported adverse events of constipation will be a review issue."

The Clinical review of this NDA will continue.

Harry Handelsman, DO
Medical Officer
Division of Reproductive and Urologic Products

Mark Hirsch, MD
Medical Leader in Urology
Division of Reproductive and Urologic Products

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/s/

Harry Handelsman
12/4/2006 04:54:02 PM
MEDICAL OFFICER

Mark S. Hirsch
12/4/2006 05:05:33 PM
MEDICAL OFFICER
I concur.