Medical Officer's Review of NDA

Fesoterodine [redacted] b(4)

NDA 22-030

Date of Submission:	**March 27, 2006**
NDA Goal Date:	**January 27, 2007**
Target Action Date:	**January 26, 2007**
Sponsor:	**Schwarz Biosciences, Inc.**

Drug Name:	
Proposed Trade Name:	[redacted] b(4)
Proposed Drug Name:	**Fesoterodine**
Pharmacologic Category:	**Anti-Cholinergic (Muscarinic Receptor Antagonist)**
Phase 3 Studies Reviewed:	**SP584, SP583 & SP686**

Indication:	**Treatment of Overactive Bladder (OAB)**
Doses Used:	**4mg & 8mg once a day**
Route of Administration	**Oral**

TABLE OF CONTENTS

1. Executive Summary.....page 3

2. Integrated Summary of Efficacy (ISE).....page 8

3. Integrated Summary of Safety (ISS).....page 14

4. Appendices.....page 33

A. Medical Officer's Review of Study SP583.....page 33
B. Medical Officer's Review of Study SP584.....page 61
C. Medical Officer's Review of Study SP686 .....page 71

I. Executive Summary

I.1. Recommendations

In the opinion of this reviewer, from a clinical perspective, fesoterodine 4mg and 8mg tablets taken once daily **should be approved** for the Sponsor's proposed indication "**treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency**" in adult men and women.

The evidence presented in the submission of this NDA is adequate in support of the effectiveness of fesoterodine. The adverse events profile of fesoterodine appears to be similar to other approved antimuscarinic drugs in its class. The safety evaluation exceeds the ICH guidance criteria for the number of patients exposed to fesoterodine and for the duration of exposure. Thorough QT safety assessment from study **SP686** showed no signal of an effect at the clinical dose of 4mg and supra-therapeutic dose of 28mg once a day on ventricular repolarization or cardiac conduction.

I.2. Summary of Clinical Findings

I.2.A. Brief Overview of Clinical Program

Fesoterodine is a new chemical entity that belongs to the class of antimuscarinic agents. Fesoterodine has been developed as a sustained release (4mg & 8mg), once daily formulation for the proposed indication of treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Fesoterodine is a non-selective muscarinic receptor antagonist. Following oral administration, fesoterodine is completely absorbed and de-esterified in vivo to the active metabolite **SPM 7605**. Maximum plasma levels of **SPM 7605** are achieved approximately 5 hours after administration of fesoterodine SR. Steady state is reached after 3 days and the major pathway for metabolism is via **CYP2D6**. Terminal half life of oral fesoterodine is approximately 7 hours. Hepatic metabolism and renal excretion contribute significantly to the elimination of **SPM 7605**. Approximately 70% of orally administered dose is recovered in urine as metabolite(s) and 7% is recovered in the feces. **SPM 7605** is distributed widely in the body, as shown by the apparent volume of distribution of 519L after IV administration of fesoterodine. The metabolites of fesoterodine other than **SPM 7605** have low or no in vitro binding to muscarinic acetylcholine receptors. In poor metabolizers of CYP2D6, exposure to SPM 7605 was approximately doubled. Inhibition of CYP3A4 by ketoconazole resulted in an approximately 2-fold increase in exposure to SPM7605. Induction of CYP3A4 by rifampin resulted in approximately 4 fold reduction in exposure to SPM 7605. No other notable drug–drug interactions have been reported.

A total of 17 Phase 1 trials in healthy patients, and three Phase 2 trials and two Phase 3 trials in patients with OAB syndrome have been conducted during the fesoterodine development program. Approximately 489 healthy subjects have received fesoterodine in Phase 1 trials and approximately 2288 patients with OAB have received fesoterodine in Phase 2 and 3 trials. In all these trials fesoterodine has been safe and well tolerated.

During the EOP2 meeting in June 2003, the sponsor was advised to conduct two, 12-week, placebo-controlled trials with micturition frequency, urge incontinence episodes and the volume voided as the key endpoints. The sponsor was also advised to conduct a thorough QT trial preferably in the target population and to perform genotyping for CYP 2D6 metabolizer status in at least one Phase 3 trial.

At the pre-NDA meeting in July 2005, the Division concurred that the sponsor had conducted the requested Phase 3 and thorough QT studies and also concurred with the sponsor's request for partial waiver/deferral for pediatric patients.

I.2.B. Efficacy

The co-primary endpoints and the key secondary endpoint for the pivotal studies are appropriate and clinically meaningful. The study results provide substantial evidence in support of effectiveness of fesoterodine 4mg and 8mg taken orally once daily for the treatment of patients 18 years and older with symptoms of overactive bladder (OAB).

The conclusions from the clinical efficacy review were as follows:

- Fesoterodine showed a statistically significant and clinically meaningful improvement in decreasing the number of micturitions during an average 24 hour period when compared to placebo over a treatment period of 12 weeks in both SP583 and SP584 trials.

b(4)

- For incontinence episode frequency, there was a clinically meaningful decrease shown in both pivotal studies and the improvements were statistically significant when compared to placebo. The improvement in incontinence episode frequency was statistically significant as early as 2 weeks after the start of treatment in both studies for the 4mg dose (the starting dose).

- For volume voided, fesoterodine increased the average volume per void in both studies. The increase was statistically significant at the $p < 0.001$ level for both fesoterodine 4mg and 8mg/day in study SP583, but only statistically significant in the 8mg dose group in study SP584.

- Fesoterodine also demonstrated a significant improvement in other clinical secondary endpoints in both Phase 3 studies.

- The magnitude of the fesoterodine treatment effect was consistent across different age groups, race and gender.

I.2.C. Safety

Safety data is primarily drawn from a total of 2288 patients with OAB who received fesoterodine SR in phase 2 and 3 trials during the drug development program. This includes 858 (38%) patients exposed to fesoterodine for >6months, 570 (25%) patients

exposed for >12 months and 162 (7%) patients exposed for >18months. There were also 489 patients that received fesoterodine during Phase 1 trials.

The overall size of the safety database and overall evaluation of safety was adequate. The reported adverse clinical events are similar to the known side effects of other approved anti-muscarnic drugs, including dry mouth, constipation, dry eyes and urinary retention. **No significant cardiovascular, hepatic, hematologic or renal toxicities were identified.**

Important safety-related findings from the clinical review were:

- Dry mouth, constipation, abdominal pain, headache, urinary retention, dry eyes and urinary tract infection were the most frequently reported adverse events that occurred in the two pivotal studies SP583 and SP584.
- Most reported clinical adverse events were mild to moderate in severity and resolved without significant medical intervention.
- The anti-muscarinic adverse events seen in the pivotal trials (i.e., dry mouth, constipation and urinary retention) appeared to be dose-related.
- A thorough clinical review of a small number of serious adverse events (SAEs) in studies **SP583** and **SP584** revealed no probable association with the use of fesoterodine. This review took into consideration cases of chest pain, angina, MI, heart failure, QTc prolongation on ECG, pneumonia, bone fractures, spinal decompression, salpingitis, appendicitis, skin disorders and abnormal LFT's. All these adverse events were mild to moderate in intensity and these patients had many co-morbid medical conditions that could have played a role in these adverse events.
- There was a modest dose-dependent increase in mean residual volume among fesoterodine-treated groups, yet this increase remained below a group average of 50mL.
- Adverse events from the use of fesoterodine that led to discontinuation included dry mouth, constipation, dry eyes, urinary retention and urinary tract infection.
- Of the 5 patients who were reported to have died during this drug program development, one patient (#10672) in study SP582 died from cerebrovascular accident, the second patient (#10527) in study SP583 died from MI, the third patient (#10943) in study SP738 died due to metastastases to the liver, the fourth patient (#11184) in study SP738 died due to "sudden death" and fifth patient (#10618) died several months after completing study SP583 due to unknown causes. Four of the five deaths were considered by the investigators to be unrelated to study medication and the fifth (the "sudden death" case) was considered "unlikely related" to study medication.

Narratives for these 5 patients, who died during fesoterodine development program, are as follows:

Patient 10672, a 76-year old female who was randomized to treatment in Phase 2 study SP582 with fesoterodine 12mg/day, suffered a fatal stroke (CVA) on Day 83. In the opinion of the investigator this fatal SAE was not related to trial medication and had a

high probability of being related to her concomitant co-morbid disease (cerebral artery sclerosis).

Patient 10527, a 70-year-old female who had been randomized to fesoterodine 8mg/day, died as a result of a heart attack (myocardial infarction) that occurred 26 days after discontinuation of trial medication during study SP583. This patient had completed the treatment period two weeks prior to hospitalization for bronchitis. Patient was discharged 8 days later from the hospital and died on following day at home. This SAE was considered by the investigator to be unrelated to trial medication.

Patient 10943, a 76-year-old female who had been taking fesoterodine 8mg/day during open-label treatment in SP738, died as a result of liver metastasis. Prior to open-label treatment, this patient had taken fesoterodine 4mg/day during SP583 for a combined double-blind plus open-label fesoterodine exposure of 254 days. The patient was diagnosed with liver metastasis and peritoneal carcinomatosis with unknown primary tumor. The patient died from the existing metastasis to liver, approximately 3 weeks after the diagnosis. No autopsy was performed. This fatal SAE was considered by the investigator to be unrelated to trial medication but most likely from a co-morbid abdominal malignancy.

Patient 11184, a 69-year-old female who had been taking fesoterodine 4mg/day for 333 days experienced an SAE of "sudden death" during open-label treatment. Prior to open-label treatment, this patient had taken fesoterodine 8mg/day during SP583. Past medical history included diabetes mellitus and asthma. During the trial, mild aortic stenosis was diagnosed. The ECGs recorded prior to, and during administration of double-blind trial medication, showed sinus rhythm and left ventricular hypertrophy. This patient died after complaining of difficulty breathing. No autopsy was performed, but the death certificate attributed her death to natural causes. Both the investigator and the sponsor considered the sudden death unlikely to be related to trial medication.

Patient 10618, an 82-year-old female who had been randomized to placebo group, died approximately 4 months after discontinuing from trial participation in study SP583. Reason for death was not provided. The investigator assessed the death as unrelated to use of trial medication.

After having reviewed the narratives above, this reviewer concurs with the investigators that none of the five deaths are related to the use of fesoterodine.

The QT safety assessment from study **SP686** demonstrated no signal of any effect of fesoterodine on the QT interval at the clinical dose of 4mg once a day and at a supra-therapeutic dose of 28mg once a day. There was no significant effect on ventricular repolarization or on cardiac conduction when compared to placebo and to the active control i.e. moxifloxacin. Fesoterodine exposure in both poor and extensive metabolizers did not increase the risk of QT prolongation.

In view of the findings from this study, this reviewer does not find any realistic risk of QT prolongation with the use of fesoterodine in patients with OAB.

I.2.D. Dosing

The 4mg and 8mg dose of fesoterodine was selected based on results from Phase 1 and Phase 2 studies. Fesoterodine given at a dose of 4mg once daily was determined by the sponsor to be the lowest effective dose in improving the symptoms of overactive bladder (OAB). However, to ensure efficacy in those patients who respond less than optimally to 4mg/day, fesoterodine dose can be titrated up to 8mg once daily. Fixed dose efficacy data for 4mg/day and 8mg/day is available from controlled clinical studies **SP583** and **SP584**, and open-label data is available for a titration regimen in the extensions studies. Fesoterodine is intended to be taken in the morning, and may be taken with or without food.

I.2.E. Special Populations

Effect on age, gender and race: Fesoterodine did not demonstrate any difference in effectiveness based on age, gender or race. There is an expected difference in anti-muscurinic adverse events between younger and older patients for this class of drugs. In general, reports of dry mouth, constipation and urinary retention are usually greater in incidence in the older population. However, in the fesoterodine trials, this was not seen. Therefore, no dosage adjustment is necessary in the older population, or based on gender or race.

Renal insufficiency: In patients with mild or moderate renal insufficiency (CL_{CR} ranging from 30-80 mL/min), C_{max} and AUC of the active metabolite are increased up to 1.5- and 1.8-fold respectively, as compared to healthy subjects. In patients with severe ($CL_{CR} < 30$ mL/min) renal insufficiency, Cmax and AUC are increased 2.0- and 2.3-fold, respectively. Therefore, based upon this information, in patients with mild or moderate renal insufficiency, no dose adjustment is recommended. Doses of fesoterodine greater than 4 mg are not recommended in patients with severe renal insufficiency.

Hepatic impairment: In patients with moderate (Child-Pugh B) hepatic impairment, Cmax and AUC of the active metabolite are increased 1.4- and 2.1-fold, respectively, as compared to healthy subjects. Therefore, based upon this modest degree of increase in maximum exposure, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. Subjects with severe hepatic impairment (Child-Pugh C) have not been studied; therefore fesoterodine is not recommended for use in these patients.

Potential for dose dumping with ETOH consumption: The Clinical and Chemistry review of the sponsor's in vitro data and the accompanying rationale demonstrates no need at this time for human clinical trials to assess the potential for dose dumping due to alcohol consumption.

Pediatric issues: Sponsor has been granted a partial waiver for conducting pediatric studies in children 5 years of age and younger, and a deferral of studies for children aged 6 to 15 years.

Use in Pregnancy Information: There are no adequate and well-controlled studies in pregnant women. As a pregnancy Category C drug, fesoterodine should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

II. Integrated Summary of Efficacy (ISE)

II.A. Brief Statement of Conclusions

Both the pivotal studies **SP583** and **SP584** were adequate and well-controlled studies conducted in Europe and the United States, respectively. Both provide substantial evidence of efficacy in the primary and key secondary efficacy variables. The primary efficacy variable were the average number of micturitions per 24 hours and the average number of urge urinary incontinence episodes per 24 hours.

The improvement in the signs and symptoms of overactive bladder (OAB) is supported by data suggesting an associated improvement in quality of life. The proposed indication therefore is well supported by the efficacy data.

II.B. Method of Efficacy Review

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

- Review of the proposed indication, study protocols, regulatory and scientific background
- Identification and review of the controlled studies to support the indication
- Conduct of a detailed review of each study for efficacy
- Detailed discussions and interactions with the Biometrics reviewer
- Generate conclusion regarding efficacy from the two pivotal studies

II.C. List of Studies, Designs, Populations and Efficacy Variables

The clinical reviewer focused on the two Phase 3 "pivotal" studies for efficacy determinations. These studies are referred to by number: **SP583** and **SP584.** The three Phase 2 studies were reviewed as well, but are not presented herein.

II.C.1. Study Designs

Both trials (**SP583** and **SP584**) were randomized, double-blind, placebo-controlled, parallel-group studies of efficacy and safety conducted at multiple centers in Europe (**SP-583**) and in the United States **(SP-584)** for a treatment duration of 12 weeks.

Both the studies **SP583** and **SP584** collected diary-based data on micturition frequency per 24 hours, urge incontinence episodes per 24 hours, and volume voided with each micturition at baseline and again at Weeks 2, 8 and 12. Week 12 was the study endpoint. Diaries were recorded for 3 days and data for volume voided was collected for 24 hours.

II.C.2. Study Populations

In study **SP583**, a total of 1135 patients were randomized and 1132 were treated: 279 with placebo, 265 with fesoterodine 4mg/day, 276 with fesoterodine 8mg/day and 283 with tolterodine 4mg/day. Most patients (>80% in any treatment group) completed the full 12 weeks of treatment. Most of patients (81%) were female. The mean patient age was 57 years with a range of 19 to 86 years. In study **SP584,** a total of 836 patients were randomized and 832 patients were treated: 266 with placebo, 267 with fesoterodine 4mg/day and 267 patients with fesoterodine 8mg/day. Most patients (>80% in any treatment group) completed full 12 weeks of treatment. Most of the patients (76%) were female. The mean age was 59 years with a range of 21 to 91 years. A total of 9% of patients were poor metabolizers for CYP2D6 by genotyping.

II.C.3. Efficacy Variables

The primary efficacy endpoints for both trials were: a) change-from-baseline in the average number of micturitions per 24 hours, and b) change-from-baseline in the average number of urge urinary incontinence episodes per 24 hours.

A key secondary endpoint was the average volume voided per micturition.

II.D. Statistical Analysis Plans (SAP)

The statistical analysis plans were consistent for both Phase 3 protocols. The critical elements of these SAPs were:

- All statistical analysis plans were finalized prior to treatment assignment
- All randomized patients with a baseline measurement were included in the efficacy analysis
- Last-observation-carried-forward (LOCF) approach was used for any missing data
- Analysis of variance (ANOVA) was planned as the test of treatment differences. The reader is referred to the Biometrics review for more details regarding the SAP and actual analyses conducted.

II.E. Efficacy Results

The following three tables (Tables 1-3) were generated by the reviewer from the data in Sponsor's study reports for Studies SP583 and SP584. Tables 1 and 2 describe the Sponsor's reported results for the primary efficacy endpoints: average number of micturitions per 24 hours and average number of urge incontinence episodes per 24 hours, respectively. Table 3 describes the Sponsor's reported results for the key secondary endpoint: average volume voided per micturition. The accompanying two figures (Figures 1 and 2) show the primary efficacy data graphically and over time.

Table 1. Micturitions per 24 hours*

	Study SP-583			Study SP-584		
	Placebo (n=279)	**Feso 4mg (n=265)**	**Feso 8mg (n=276)**	**Placebo (n=266)**	**Feso 4mg (n=267)**	**Feso 8mg (n=267)**
Baseline	12.0(3.7)	11.6(3.2)	11.9(3.8)	12.2(3.7)	12.9(3.9)	12.0(3.3)
Endpoint	10.9(4.2)	9.8(3.1)	10.0(4.4)	11.2(3.4)	11.0(3.6)	10.1(3.2)
Change from baseline	-1.02(3.0)	-1.74(2.7)	-1.94(3.1)	-1.02(3.4)	-1.86(3.6)	-1.94(3.0)
P-value for change from baseline vs. placebo		P<0.001	P<0.001		P=0.032	P<0.001

*Data presented as Mean (SD). Sample size reflects number of patients at baseline. P-value derived from analysis of the variance test using baseline to endpoint difference and LOCF.

Figure 1. Change from baseline in frequency of micturitions per 24 hours

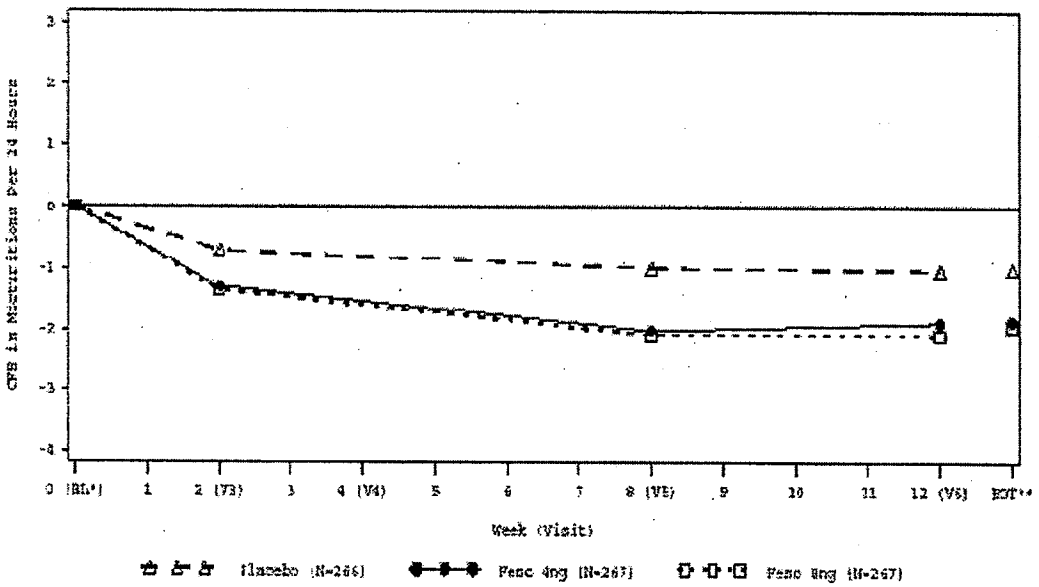


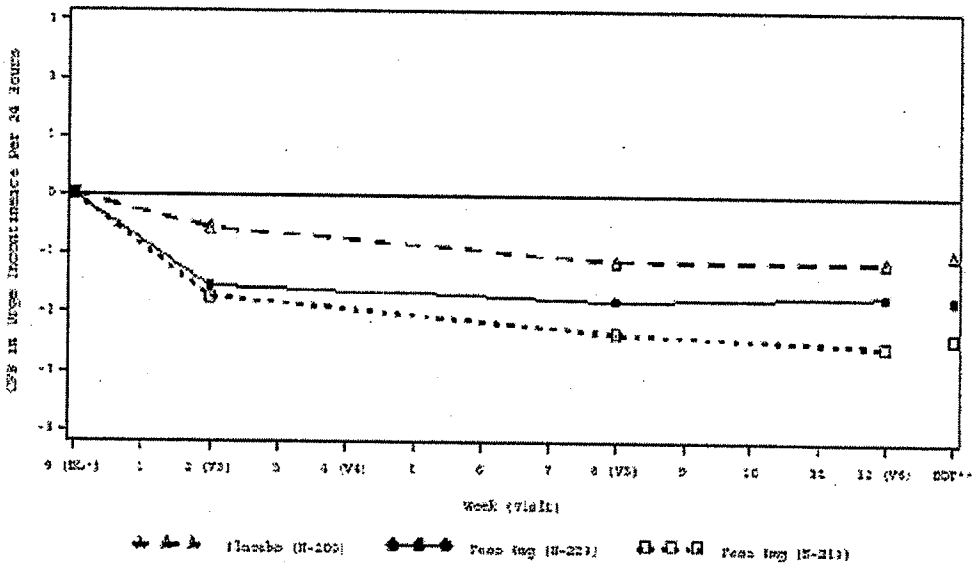
Table 2. Incontinence episodes per 24 hours*

	Study SP-583			Study SP-584		
	Placebo (n=211)	**Feso 4mg (n=199)**	**Feso 8mg (n=223)**	**Placebo (n=205)**	**Feso 4mg (n=228)**	**Feso 8mg (n=218)**
Baseline	3.7(3.1)	3.8(3.4)	3.7(2.9)	3.7(3.3)	3.9(3.5)	3.9(3.3)
Endpoint	2.5(3.5)	1.8(2.9)	1.4(2.5)	2.7(3.3)	2.1(3.2)	1.4(2.1)
Change from baseline	-1.20(3.3)	-2.06(2.7)	-2.27(2.4)	-1.0(2.7)	-1.77(3.1)	-2.42(2.8)
P-value for change from baseline vs. placebo		P=0.001	P<0.001		P=0.002	P<0.001

* Data presented as Mean (SD). Sample size reflects number of patients at baseline. P-value derived from analysis of the variance test using baseline to endpoint difference and LOCF.

Figure 2.

Change from Baseline in average number of urge incontinence episodes per 24 hours for each visit by randomized treatment population (FAS in SP584)



CFB=change from Baseline, FAS=full analysis set, Feso=Fesoterodine, LOCF=last observation carried forward

Table 3. Volume voided per micturition*

	Study SP-583			Study SP-584		
	Placebo (n=279)	**Feso 4mg (n=265)**	**Feso 8mg (n=276)**	**Placebo (n=266)**	**Feso 4mg (n=267)**	**Feso 8mg (n=267)**
Baseline	150.2(52.0)	160.0(59.5)	153.9(56.9)	159.4(69.0)	152.0(60.2)	155.9(57.7)
Endpoint	159.9(62.0)	187.0(92.6)	187.5(73.7)	167.5(95.7)	169.5(78.0)	189.3(77.3)
Change from baseline	9.8(43.5)	27.0(70.3)	33.5(54.2)	7.9(69.4)	17.0(61.1)	33.4(62.5)
P-value (Δ baseline vs. placebo)		P=<0.001	P<0.001		P=0.15	P<0.001

*Data presented as Mean (SD). Sample size reflects number of patients at baseline. P-value derived from analysis of the variance test using baseline to endpoint difference and LOCF.

II.E.1. Summary of efficacy results

In the primary efficacy trials, fesoterodine 4 and 8mg administered once daily for 12 weeks improved both the two primary and key secondary efficacy variables. All three key variables as shown above in tabular format (**change in the average number of micturitions per 24 hours, change in the average number of urge incontinence episodes per 24 hours, and volume voided**) improved in a dose-responsive, statistically significant manner compared to placebo treatment. b(4)

The diary endpoints were explored further by other analyses. One method of exploring the data was to calculate the number of "continent days" achieved. Treatment with fesoterodine increased the mean number of continent days per week in a dose-dependent manner during both studies and this benefit appeared to continue in the long-term extension trials. Increases in mean number of continent days per week were observed at the first post-dose visit, 2 weeks after the initiation of trial medication. Overall, patients who were receiving fesoterodine in these trials gained a mean of about 2 to 3 continent days per week and this effect appeared to be maintained in long-term, opne-label treatment.

Fesoterodine use decreased (improved) the mean number of total voids per 24 hours during both Phase trials and also in the Phase 2 dose-ranging trials. Decreases in mean number of total voids per 24 hours were observed at the first post-dose visit, b(4)

Data from long-term, open-label extension trials provide additional support for these results from these Phase 3 pivotal studies of fesoterodine.

II.E.2. Efficacy results by age
Subgroup analyses of the 3 key variables by age showed no substantial differences compared to the primary comparisons. Consistent with the primary analysis, all subgroups, regardless of age responded in a more pronounced manner to fesoterodine than to placebo. A dose-responsive effect was observed for fesoterodine 4 and 8mg/day. Overall, **the response to fesoterodine was similar in all age groups** analyzed.

II.E.3. Efficacy results by gender
Subgroup analyses of the key variables by gender showed no substantial differences compared to the primary comparisons. Overall, the response to fesoterodine was similar among males and females. In addition, gender did not influence the pharmacokinetics of fesoterodine, as supported by results of population pharmacokinetic analyses. Based on efficacy and pharmacokinetic results, **no dosage adjustment based on gender is necessary**.

II.E.4. Efficacy results by race
Subgroup analyses of the key variables by race showed no substantial differences compared to the primary comparisons. Consistent with the primary analysis, all subgroups studied, regardless of race, responded in a more pronounced manner to fesoterodine than to placebo. The only exception to this was in change from baseline in number of micturitions per 24 hours at the fesoterodine 8mg/day dose in the non-White subgroup, where the improvement was less than that observed with placebo. The effects of fesoterodine 4mg/day and tolterodine were more pronounced than for placebo, however, there was a relatively high placebo response for this parameter, and a relatively limited population for each treatment arm. Therefore, this was no considered to be a clinically meaningful finding.

Based on efficacy and pharmacokinetic results, **no dosage adjustment is necessary in this population group.**

II.F. Efficacy Conclusions
The pivotal studies **(SP-583 and SP-584)** showed statistically significant changes from baseline in both primary endpoints (number of micturitions per 24 hours and number of urge incontinence episodes per 24 hours) and in the key secondary endpoint (volume voided per micturition) when compared to placebo for a period of 12 weeks. The improvement was evident as early as ——— from the commencement of the treatment. The results were similar in magnitude and consistent for the two primary endpoints and the key secondary endpoint in both trials. The results were similar regardless of patients' age, gender or race. Exploratory secondary endpoints also supported the benefit of fesoterodine for the treatment of this condition.

b(4)

Therefore, in the opinion of this reviewer, the effectiveness of fesoterodine is well supported by results from the controlled studies.

III. Integrated Summary of Safety (ISS)

III. A. Brief Statement of Conclusions

The adverse event profile of fesoterodine appears to be similar to that of other antimuscrinic drugs. Dry mouth, constipation and urinary retention were the most frequently reported events in the pivotal studies **(SP583 and SP584).** These adverse events were mild to moderate in intensity. The other less frequently reported but clinically significant adverse events associated with fesoterodine were urinary tract infection, karato-conjunctivitis sicca (dry eyes), headache, nasopharyngitis and hypertension.

No hepatotoxicity was reported in any trials of fesoterodine, although there were a few patients with mild increase in serum transaminase levels, but <3X ULN. There was no determination of a direct association between these increases in transaminase levels and fesoterodine. These events will be labeled. There is no evidence of renal toxicity in association with fesoterodine.

No apparent QT safety signal was identified among patients in the pivotal studies **SP-583** and **SP584**. **Study SP686** was specifically designed and conducted to study the effect of fesoterodine on cardiac repolarization. The study was adequately powered and included a positive control, as recommended in the FDA draft guidance document. This trial, in evaluating the effects of fesoterodine at both therapeutic and supra-therapeutic doses (4mg and 28mg once daily), showed that fesoterodine resulted in no significant cardiac repolarization or cardiac conduction when compared to placebo and the active control moxifloxacin. However, there was a mild-moderate increase in heart rate following treatment in the high dose group. This increase in heart rate was asymptomatic, appeared to pose no specific cardiac risk, and will be labeled.

In view of all the facts summarized above, **fesoterodine is considered to be safe** at doses of 4mg and 8mg twice daily given orally to patients with OAB.

III.B. Description of Patient Exposure and Demographics

The pivotal study **SP583** was conducted at 16 European sites and 1135 patients with OAB were enrolled. A total of 541 patients received the study treatment: fesoterodine 4mg (n=265) once daily and fesoterodine 8mg (n=276) once daily. 279 patients received placebo and 283 patients got tolterodine 4mg once daily as an "active control" for 12 weeks.

The second pivotal study **SP584** was conducted at multiple US sites and 1587 patients with OAB were enrolled. 836 patients were randomized and a total of 832 patients received the study treatment: fesoterodine 4mg (n=282) once daily and fesoterodine 8mg (n=279) once daily. 271 patients received placebo for the duration of 12 weeks.

In both studies, the patient population was predominantly female (76%) and mean age group was approximately 59 years (21-91 years). In the second pivotal, where genotyping was done routinely, 10% of the patient population were poor metabolizers for CYP2D6.

III.C. Method of Integrated Safety Review

The reviewer conducted detailed analyses of safety from each of the two listed pivotal trials that included each of the following items:

- Deaths
- Serious adverse events
- Medically significant adverse events
- Overall treatment emergent adverse events
- Discontinuation of study medication due to adverse events
- Laboratory findings
- Vital signs and ECG findings
- Special safety concerns
- Antimuscarinic side effects

In addition, the reviewer analyzed the sponsor's integrated summary of safety from both the original NDA and the 120-Day Safety Update for the same parameters as those listed above.

III.D. Safety Results

III.D.1. Deaths

As of the submission of this NDA and all safety updates thereafter, a total of **5 deaths** was reported in all placebo and active controlled studies. None of these deaths were judged by the investigator to be related to the study medication.

Of the 5 patients who have died during this drug program development, one patient (#10672) in study SP582 died from cerebrovascular accident, the second patient (#10527) in study SP583 died from MI, the third patient (#10943) in study SP738 died due to metastastases to liver, the fourth patient (#11184) in study SP738 died due to "sudden death", and fifth patient (#10618) died several months after completing study SP583 due to unknown causes. Four of the five deaths were considered by the investigators to be unrelated to festerodine. The "sudden death" case was considered unlikely related to the trial medication.

Table 4.

Subjects who had adverse events with fatal outcomes

Trial number/ subject number	Dose and duration of trial medication at onset of AE	Preferred term/ reported term	Causality (per investigator)
SP582/ 10672	Fesoterodine 12mg/day for 83 days	Cerebrovascular disorder/ stroke	Not related
SP583/ 10527	NA[a]	Myocardial infarction/ heart attack	Not related
SP738/ 10943	Fesoterodine 8mg/day for 254 days	Metastases to liver/ liver metastasis	Not related
SP738/11184	Fesoterodine 4mg/day for 333 days	Sudden death/ sudden death	Unlikely
SP583/ 10618	NA[b]	NA	Not related

AE=adverse event, NA=not applicable

Case narratives for these 5 patients, who died during the fesoterodine development program, are as follows:

Patient 10672, a 76-year old female who was randomized to treatment in study SP582 with fesoterodine 12mg/day, suffered a fatal stroke (CVA) on Day 83. In the opinion of the investigator this fatal SAE was not related to trial medication and had a high probability of being related to her concomitant co-morbid disease (cerebral artery sclerosis).

Patient 10527, a 70-year-old female who had been randomized to fesoterodine 8mg/day, died as a result of a heart attack (myocardial infarction) that occurred 26 days after discontinuation of trial medication during study SP583. This patient had completed the treatment period two weeks prior to hospitalization for bronchitis. Patient was discharged 8 days later from the hospital and died on following day at home. This SAE was considered by the investigator to be unrelated to trial medication.

Patient 10943, a 76-year-old female who had been taking fesoterodine 8mg/day during open-label treatment in SP738, died as a result of liver metastasis. Prior to open-label treatment, this patient had taken fesoterodine 4mg/day during SP583 for a combined double-blind plus open-label fesoterodine exposure of 254 days. The patient was diagnosed with liver metastasis and peritoneal carcinomatosis with unknown primary tumor. The patient died from the existing metastasis to liver, approximately 3 weeks after the diagnosis. No autopsy was performed. This fatal SAE was considered by the investigator to be unrelated to trial medication but most likely from a co-morbid abdominal malignancy.

Patient 11184, a 69-year-old female who had been taking fesoterodine 4mg/day for 333 days experienced an SAE of "sudden death" during open-label treatment. Prior to open-label treatment, this patient had taken fesoterodine 8mg/day during SP583. Past medical

history included diabetes mellitus and asthma. During the trial, mild aortic stenosis was diagnosed. The ECGs recorded prior to, and during administration of double-blind trial medication, showed sinus rhythm and left ventricular hypertrophy. This patient died after complaining of difficulty breathing. No autopsy was performed, but the death certificate attributed her death to natural causes. Both the investigator and the sponsor considered the sudden death unlikely to be related to trial medication.

Patient 10618, an 82-year-old female who had been randomized to placebo group, died approximately 4 months after discontinuing from trial participation in study SP583. Reason for death was not provided. The investigator assessed the death as unrelated to use of trial medication.

> ***Reviewer's Comment: This clinical reviewer agrees with the assessment of the investigators in these cases, that none of the five deaths that occurred during the development of this drug were related to the study medication. One death was from the placebo group and the other four had co-morbidities that either directly contributed to their death (e.g. liver metastases)or co-morbidities that could have contributed to the fatal outcomes.***

Addendum:
As per a recent adverse event report submitted by the sponsor on Oct. 25, 2006, there was one more event of death that occurred "due to natural causes" in a 76 year old female who received fesoterodine during SP739, an open label trial for the treatment of OAB. The patient had been on fesoterodine for at least fifteen plus months before the event occurred. The patient also received concomitant medications for co-morbid medical conditions. This event of death was determined to be unrelated to the study medication by the investigator.

> ***Reviewer's Comment: From the brief adverse event report submitted by the sponsor, this clinical reviewer concurs with the opinion of the investigator.***

III.D.2. Serious Adverse Events (SAEs)
In the controlled clinical trials combined, SAE's were reported in patients treated with placebo, fesoterodine 4mg, 8mg, 12mg/day;or tolterodine 4mg/day in 2%, 4%, 3%, 6%; and 2% of patients in these treatment groups. Serious AE's in all treatment groups occurred across multiple body systems with no obvious trends. Serious AEs reported by more than 1 patient in any fesoterodine-treated group included: chest pain/angina (in 3 patients), pneumonia, asymptomatic QTc interval prolongation as seen on ECG, appendicitis, and salpingitis (in 2 patients each). Other SAE types were reported in only 1 patient each.

In the primary safety pool, drug-related SAE's (as determined by the investigator) occurred in 2% of patients in the fesoterodine 12mg/day group, and in ≤1% of patients in all other groups, including the to-be-marketed 4mg and 8mg per day groups. Angina

pectoris (n=2 patients) was the only drug-related SAE that occurred in more than 1 patient in Pool S1.

During long-term open-label treatment, SAE's occurred in 9% of patients. Serious AEs reported by more than 2 patients each during open-label treatment included: myocardial infarction (in 4 patients [<1%]); and breast cancer, bronchitis, knee arthroplasty, and cholecystectomy (in 3 patients each).

Table 5. List of non-fatal SAE's in study SP583

Patient#	Age/ Gender	SAE	Dose/Day	Intensity	Causality
10048	72/M	Femoral neck fracture	4mg	Moderate	Not related
10055	49/F	Asthma	4mg	Moderate	Not related
10125	54/F	Hip arthroplasty	8mg	Severe	Not related
10258	72/M	QT prolongation on ECG	8mg	Mild	Possible
10288	70/M	Angina pectoris	Placebo	Severe	Possible
10339	72/F	Unstable angina	8mg	Severe	Unlikely
10472	78/F	Tibia fracture	Placebo	Severe	Not related
10480	58/F	Heart failure	4mg	moderate	Not related
10527	70/F	Bronchitis MI	8mg 0mg	Severe Severe	Not related Not related
10535	60/F	QT prolongation on ECG	8mg	Mild	Unlikely
10618	82/F	Fracture patella Depression Death	Placebo Placebo Placebo	Severe Severe Severe	Not related Not related Not related
10700	53/F	Basedow's disease	4mg	Mild	Not related
10715	30/F	Salpingitis	4mg	Moderate	Not related
10766	52/F	Gastroentritis	4mg	Severe	Possible
10806	58/F	Dyspepsia	4mg	Moderate	Unlikely
10874	63/M	Pneumonia	8mg	Severe	Unlikely
10885	50/F	Eczema	Placebo	Mild	Not related
11034	54F	Depression	4mg	Moderate	Not related
11037	66/M	Cholithiasis	Placebo	Severe	Unlikely
11048	75/F	Arthalgia Joint dislocation	Placebo Placebo	Moderate Moderate	Not related Not related
11126	72/F	Breast surgery	8mg	Mild	Not related
11159	25/F	Abdominal pain	4mg	Moderate	Not related
11185	68/F	Sciatica	8mg	Moderate	Unlikely
11328	48/F	Chest pain	4mg	Mild	Possible
11348	52/F	Endometrial hypertrophy	8mg	Mild	Not related
11410	54/F	Abnormal labs	Placebo	Mild	Not related
11446	47/F	Implant complication	4mg	Moderate	Not related

Table 6: List of Non-fatal SAE's In SP584

Patient #	Age/ Gender	SAE	Dose/Day	Intensity	Causality
13017	47/F	Appendicitis	4mg	Moderate	Not related
13066	58/F	Sinusitis	8mg	Severe	Not related
13316	61/F	Pneumonia	Placebo	Moderate	Not related
13551	61/F	Chest pain	4mg	Severe	Not related
13809	46/F	Spinal decompression	4mg	Moderate	Not related
14131	62/M	Malignant melanoma	4mg	Severe	Not related
14190	67/F	Abnormal LFT's	Placebo	Severe	Not related
14207	64/F	Brain neoplasm	8mg	Mild	Unlikely
14330	42/F	Viral gastroentitis	8mg	Severe	Not related
14505	66/F	Knee arthroplasty	8mg	Moderate	Not related
14583	68/F	Ankle fracture	4mg	Moderate	Unlikely
14703	49/F	Colitis	4mg	Severe	Not related
14716	47/F	Rotator cuff repair	8mg	Severe	Not related
14776	62/M	Thoracotomy	4mg	Severe	Not related
14861	58/F	Cataract	4mg	Severe	Not related

***Reviewer's Comment:** This clinical reviewer concurs with the fact that there were no serious adverse events as a direct result of fesoterodine use. However, there were other existing co-morbidities in those patients using fesoterodine 4mg and 8mg/day that may have led to some of the SAEs listed in the previous two tables.*

III.D.3. Other Medically Significant Adverse Events

There were no other medically significant adverse events in fesoterodine-treated groups in the pivotal studies **SP583** and **SP584.** However, a clinical adverse event report was recently submitted by the sponsor, described as an event of **"pancreatitis"** that occurred in a 72 year old female, who received fesoterodine for 16 months during **SP739 trial (an open-label extension of SP584).** The patient had history of cholecystectomy and other co-morbid medical conditions and was also on other concurrent medications. The event was determined by the investigator as unlikely related to fesoterodine.

***Reviewer's Comment:** Based on the adverse event report submitted, this clinical reviewer agrees with the investigator's report that the adverse event of pancreatitis is not likely related to fesoterodine.*

III.D.4. Overall Adverse Events

Commonly reported AE's that occurred more often in patients treated with fesoterodine than placebo included: dry mouth, constipation, urinary tract infection, dyspepsia, lacrimal disorder (dry eye), dry throat, dysuria, abdominal pain upper, nasopharyngitis, and back pain. Except for urinary tract infection, nasopharyngitis, and back pain, AEs were reported more often in the fesoterodine 12mg/day group than in the fesoterodine 4 mg/day or 8mg/day treatment groups.

Table 7. List of AEs reported in pooled Studies SP583 and SP584

Treatment-emergent adverse events reported by ≥2% of subjects in any fesoterodine treatment group (Pool S1)

Preferred term	Placebo N=780 n (%)	Feso 4mg/day N=782 n (%)	Feso 8mg/day N=785 n (%)	Feso 12mg/day N=222 n (%)	Tolt 4mg/day N=290 n (%)
Dry mouth	65 (8)	173 (22)	275 (35)	113 (51)	49 (17)
Headache	59 (8)	64 (8)	49 (6)	34 (15)	14 (5)
Constipation	19 (2)	28 (4)	47 (6)	18 (8)	8 (3)
Urinary tract infection	22 (3)	26 (3)	32 (4)	5 (2)	4 (1)
Dyspepsia	4 (<1)	12 (2)	25 (3)	6 (3)	5 (2)
Lacrimal disorder (dry eye)	1 (<1)	10 (1)	23 (3)	6 (3)	1 (<1)
Nausea	24 (3)	17 (2)	18 (2)	15 (7)	6 (2)
Dry throat	4 (<1)	8 (1)	17 (2)	14 (6)	3 (1)
Dysuria	8 (1)	12 (2)	16 (2)	8 (4)	3 (1)
Abdominal pain upper	8 (1)	11 (1)	16 (2)	7 (3)	3 (1)
Nasopharyngitis	23 (3)	28 (4)	13 (2)	7 (3)	10 (3)
Back pain	9 (1)	19 (2)	12 (2)	2 (<1)	1 (<1)
Diarrhea	16 (2)	18 (2)	11 (1)	6 (3)	3 (1)
Upper respiratory tract infection	16 (2)	16 (2)	10 (1)	3 (1)	2 (<1)
Influenza	19 (2)	25 (3)	7 (<1)	4 (2)	2 (<1)
Dizziness	18 (2)	17 (2)	9 (1)	8 (4)	4 (1)
Abdominal pain	13 (2)	6 (<1)	7 (<1)	8 (4)	5 (2)
Cough	13 (2)	17 (2)	8 (1)	6 (3)	5 (2)
Asthenia	6 (<1)	2 (<1)	5 (<1)	5 (2)	2 (<1)
Chest pain	5 (<1)	8 (1)	4 (<1)	5 (2)	1 (<1)
Dysgeusia	6 (<1)	4 (<1)	4 (<1)	7 (3)	0
Vision blurred	8 (1)	3 (<1)	4 (<1)	5 (2)	2 (<1)
Nasal dryness	3 (<1)	7 (<1)	3 (<1)	7 (3)	2 (<1)

Feso=fesoterodine, Tolt=tolterodine

AE's were reported for 23% of patients in the placebo group; 35%, 46%, and 64% of patients in the fesoterodine 4, 8, and 12mg/day groups, respectively. As expected, many of the AE's were dry mouth, constipation, lacrimal disorder (dry eye), dyspepsia, and abdominal pain. These are commonly seen with the use of anti-muscarinic drugs. Initial onset of drug-associated AE's usually occurred within the first month of treatment.

Overall 23%, 33%, 47%, and 64% of patients in the placebo, fesoterodine 4mg/day,

fesoterodine 8mg/day, and fesoterodine 12mg/day groups, respectively had AEs considered by the investigator to be drug related. Dry mouth, constipation, headache, and dry throat were considered to be drug related in at least 5% of patients in any fesoterodine treatment group.

Most AE's were mild or moderate in intensity. Severe AE's were reported for 4%, 5%, 8%, and 14% of patients in the placebo; and fesoterodine 4, 8, and 12mg/day groups, respectively. Dry mouth was the AE most often rated as severe in intensity (<1%, <1%, 3%, and 9% in the placebo; and fesoterodine 4, 8, and 12mg/day groups, respectively.

With long-term fesoterodine treatment in the open-label extension studies, the profile of common AE's was similar to that listed above for Pool S1. With long-term treatment, severe AEs were reported for 14% of patients. Severe dry mouth (4%) and severe constipation (1%) were the only severe AEs reported by ≥1% of patients in Pool S2.

> ***Reviewer's Comment**: It is the impression of this reviewer that the overall adverse events reported by fesoterodine-treated patients during these trials were generally mild and typical adverse events for the anti-muscurinic class of medications. In this study, all AE's resolved without any further medical intervention.*

III.D.5. Discontinuation of Study Medication Due to AE's

A total of 142 patients in Pool S1 discontinued due to AEs during treatment: 26/780 (3%) in the placebo group; and 35/782 (5%), 45/785 (6%), and 27/222 (12%) patients in the fesoterodine 4, 8, and 12mg/day groups respectively. The incidence of discontinuations due to dry mouth were similar in the placebo, fesoterodine 4 and 8mg/day groups, and tolterodine 4mg/day treatment groups (<1% in each group).

Discontinuations due to dry mouth rose to 5% in the fesoterodine 12mg/day group. Other than dry mouth there was no clear dose-dependent relationship between fesoterodine and frequency of discontinuations due to any particular AE. Two AE's, "mucosal dryness" and constipation, resulted in 2 (<1%) and in 3 (<1%) patients respectively, discontinuing treatment with fesoterodine 8mg/day, but led to no treatment withdrawals in the fesoterodine 4 or 12mg/day groups. The preferred term "blurred vision" led to treatment withdrawals in the fesoterodine 12mg/day group only (<1%).

Adverse events led to discontinuation of fesoterodine in 11% of patients during long-term treatment. These AEs were typical of those seen during treatment with anti-muscarinics, and included (in more than 2 patients during OL treatment): dry mouth in 16 (2%) patients, urinary retention in 10 (<1%) patients, constipation in 8 (<1%) patients, residual urine volume in 6 (<1%) patients, lacrimal disorder (dry eye) in 5 (<1%) patients, and urinary tract infection, cough, dry throat, and dry skin in 3 (<1%) patients each. Serious AE's led to the discontinuation of 17/1055 (2%) patients during OL treatment. No single SAE led to discontinuation in more than 1 patient during OL

treatment. Taken together, **the long-term data from the open-label periods of these trials did not identify any safety concerns leading to discontinuation of study drug.**

III.D.6. Summary of Clinical Laboratory Findings

Overall, there were no apparent trends in mean changes from baseline to the end of treatment or in shifts of clinical relevance over time in any hematology, clinical chemistry, or urinalysis parameters. Examination of individual clinically-relevant laboratory abnormalities showed that there was no clinically relevant pattern of laboratory abnormalities reported as AE's that resulted in withdrawal. Likewise, while there were individual cases that exceeded the normal range for individual laboratory parameters, there were no trends in occurrence of markedly abnormal laboratory findings.

With respect to serum transaminases in particular, no more than 6% of fesoterodine-treated patients in the primary safety pool (Pool S1) had an abnormal hepatic laboratory parameter that was above the upper limit of normal (ULN) during treatment and the proportion of patients who met this criterion was similar between all treatment groups, including placebo. There were isolated cases of mild to moderate elevations in AST, ALT, and GGT. Similar proportions of patients in all treatment groups met the 2.5 X ULN criterion. No fesoterodine-treated patient in Pool S1 or Pool S2 had an AST/ALT elevation above 2.5 - 3.0 X ULN with bilirubin also above ULN.

Very few patients in any of the treatment groups had a laboratory abnormality reported as an AE during treatment.

In regard to hematology parameters, there were no apparent trends of clinical concern in marked abnormalities in either Pool S1 or Pool S5. In general, marked hematology abnormalities occurred in no more than 3% of festerodine-treated patients at either 1, 2 or 3 months after treatment. Similar results were observed in the placebo and tolterodine treatment groups. In regard to chemistry parameters, marked abnormalities occurred in no more than 4% of fesoterodine-treated patients at either 1, 2 or 3 months after treatment. Similar results were observed in the placebo and tolterodine treatment groups.

In regard to renal laboratory parameters, there was a single adverse event of "**renal impairment**" that was reported for 1 patient in Pool S1 on the basis of abnormal laboratory values. This patient, **#14569** from **SP584,** had an AE that was reported as "abnormal kidney function (per labs)." This patient had elevated BUN starting at the baseline visit, and elevated uric acid at every visit including screening. The patient's creatinine values were at or near the ULN value (1.20mg/dL) at all visits, with the highest value being (1.20mg/dL) reported at the baseline visit. This adverse event was ongoing until the end of the trial with no clinical significance.

In regard to hepatic laboratory parameters, there were isolated cases of l**iver enzyme elevations** reported as AEs leading to discontinuation in Pool S1 and Pool S5. Laboratory-related AE led to discontinuation in 3 fesoterodine-treated patients (increased GGT in 3 fesoterodine-treated patients [fesoterodine 4mg/day: 1 patient; fesoterodine 8mg/day: 2 patients]) and 1 placebo-treated patient. Brief narratives for these

fesoterodine-treated patients who discontinued treatment due to laboratory-related AEs are provided below:

Study 584/patient #13322, a 54-year-old Caucasian male, experienced increased GGT level. At the time of the AE, the patient was taking fesoterodine 4mg/day. His GGT level steadily increased from Visit 1 through the safety follow-up visit. The patient had begun consuming excessive amounts of alcohol during the trial and discontinued the trial at Visit 4. The AE was considered not resolved at the end of the trial.

Study 584/patient #3764, a 36-year-old Hispanic female, experienced AE of increased ALT, AST, and GGT while on 8mg/d of fesoterodine for 56 days. Due to the elevated level of GGT the investigator stated this was clinically relevant and discontinued the patient from the trial. Lab results collected at the safety f/u visit showed a decrease of all 3 lab values. ALT and AST increase fully resolved, however the increased GGT level still remained elevated until the last follow up. All 3 AEs were considered mild in intensity. Total bilirubin and alkaline phosphatase were within normal ranges throughout the trial.

Study 584/patient # 14011, a 66-year-old Caucasian male, experienced increased GGT level. At the time of the AE that led to withdrawal, the patient was taking fesoterodine 8mg/day and had been at that dose for 16 days. At Visit 3, the patient developed an increase in GGT. Laboratory tests were repeated 4 and 10 days later that showed a decrease in GGT towards normal range. AST, ALT, and total bilirubin values were within normal range during the entire trial. This event was reported as a non-serious AE and the investigator assessed the elevated GGT to be possibly related to trial medication.

In addition, there were 2 other hepatic laboratory-related SAEs that led to discontinuation. One patient in study **SP582** had an SAE of hepatocellular involvement by metastatic disease and 1 patient in study **SP583** that had an SAE of cholelithiasis.

In Pool S1 and Pool S5, there were no patients with any AST/ALT elevation above 2.5 X ULN in conjunction with bilirubin above ULN, as is evident from the following two tables:

Tables 8 and 9.

Summary of fesoterodine-treated subjects with increased hepatic function analytes above ULN cutpoints (Pool S1)

Para-meter	ULN cutpoint	Trial/Subject Number	Age/ Gender	Treatment Group	AE? Y/N	Withdrew? Y/N	Resolved? Y/N
ALT	2.5 X ULN	SP582/10002	64/M	Feso 4mg/day	Y[a]	N	Y
		SP582/10384[b]	31/M	Feso 4mg/day	N	N	NA[c]
		SP582/11979[d]	35/F	Feso 8mg/day	Y[e]	Y	Y
		SP583/10894[f]	64/M	Feso 4mg/day	N	N	NA[c]
		SP583/11420	41/F	Feso 4mg/day	Y	N	Y
AST	2.5 X ULN	SP582/11979[d]	35/F	Feso 8mg/day	Y[e]	Y	Y
		SP583/10894[f]	64/M	Feso 4mg/day	N	N	NA[c]
		SP583/11420	41/F	Feso 4mg/day	Y	N	Y
GGT	3 X ULN	SP583/11034[g]	54/F	Feso 4mg/day	N	N	NA[c]
		SP583/11165[h]	62/F	Feso 8mg/day	Y	N	Y

AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, F=female, GGT=gamma-glutamyl transferase, M=male, NA=not applicable, N=no, SAE=serious adverse event, ULN=upper limit of normal, Y=yes

Summary of fesoterodine-treated subjects with increased hepatic function analytes above ULN cutpoints in US trials SP668 and SP584 (Pool S1)

Para-meter	ULN cutpoint	Trial/Subject Number	Age/ Gender	Treatment Group	AE? Y/N	Withdrew? Y/N	Resolved? Y/N
ALT	2.5 X ULN	SP584/14170[a]	59/F	Feso 4mg/day	N	N	NA[b]
		SP584/14460	48/F	Feso 4mg/day	N	N	NA[b]
		SP584/14732	48/F	Feso 4mg/day	N	N	NA[b]
		SP584/13764[a]	36/F	Feso 8mg/day	N	N	NA[b]
		SP584/14190[c]	67/F	Feso 8mg/day	Y[d]	N	N
AST	2.5 X ULN	SP584/13196	51/M	Feso 8mg/day	Y	N	Y
		SP584/14190[c]	67/F	Feso 8mg/day	Y[d]	N	N
AP	3 X ULN	SP584/14190[c]	67/F	Feso 8mg/day	Y[d]	N	N
GGT	3 X ULN	SP584/13322[a]	54/M	Feso 4mg/day	N	N	NA[b]
		SP584/14011	66/M	Feso 8mg/day	Y	Y	Y
		SP584/14190[c]	67/F	Feso 8mg/day	Y[d]	N	N
		SP584/14273	77/F	Feso 8mg/day	N	N	NA[b]
		SP584/14605	47/F	Feso 8mg/day	N	N	NA[b]
		SP668/12188	74/F	Feso 8mg/day	N	N	NA[b]

AE=adverse event, ALT=alanine aminotransferase, AP=alkaline phosphatase, AST=aspartate aminotransferase, F=female, GGT=gamma-glutamyl transferase, M=male, NA=not applicable, N=no, SAE=serious adverse event, ULN=upper limit of normal, Y=yes

Reviewer's comment: ***It is the opinion of this reviewer that in general, hematology, chemistry and urinalysis were similar between festerodine (4mg and 8mg), placebo and tolterodine group in study SP583. However, there was mild increase (<2XULN) in transaminase levels in few patients in Pool S1***

(SP582, SP668, SP583and SP584), that did not translate into a clinically meaningful effect. These very infrequent and modest increases in serum ALT and AST will be displayed in the Adverse Reactions section of the label.

III.D.7. Vital Signs and ECGs

III.D.7.1. Vital Signs

No clinically relevant changes from baseline were observed for systolic BP, diastolic BP, or pulse rate. Blood pressure was relatively stable from baseline to end of treatment. As summarized in the following table, a slight dose-dependent increase in mean pulse rate from baseline to end of treatment occurred in all the fesoterodine treatment groups in both Pool S1 and Pool S5. The proportions of patients with changes in blood pressure were similar across treatment groups.

Table 10.

Mean change from Baseline to end of treatment in pulse rate

Treatment Group	Pool S1 Mean (SD) N=2859	Pool S5 Mean (SD) N=1964
Placebo	0.47 (9.15)	0.46 (9.24)
Fesoterodine 4mg/day	2.06 (9.39)	2.43 (9.19)
Fesoterodine 8mg/day	3.07 (9.69)	3.49 (9.67)
Fesoterodine 12mg/day	3.02 (11.50)	--
Tolterodine 4mg/day	2.07 (8.70)	2.07 (8.70)

SD=standard deviation

III.D.7.2. ECGs

At the end of treatment in Pool S1, ECG recordings revealed a mean increase (3-6bpm) in heart rate, was observed in patients receiving fesoterodine and tolterodine compared with a mean increase of <1bpm in the placebo group. QTc values were calculated according to the Fridericia and Bazett formulas. When analyzed according to the Fridericia method, there were no differences among treatment groups in QTcF at the end of treatment compared to baseline. As expected, when analyzed according to the Bazett formula, small (2-4ms) mean increase from baseline was seen in the fesoterodine treatment group and in the tolterodine 4mg/day group compared to a small decrease in the placebo group. For PR interval and QT interval, small reductions from baseline were observed in all treatment groups consistent with the increase in heart rate. There were no relevant mean changes from baseline in QRS duration. In Pool S5, ECG results were generally similar to results in Pool S1

Table 11.

Change from Baseline at end of treatment in 12-lead electrocardiogram results (Pool S1 and Pool S5)

Parameter	Placebo Mean (SD)	Feso 4mg/day Mean (SD)	Feso 8mg/day Mean (SD)	Feso 12mg/day Mean (SD)	Tolt 4mg/day Mean (SD)
Pool S1 (at EOT)	N=768	N=774	N=771	N=216	N=285
Heart rate (bpm)	0.7 (7.88)	3.5 (9.38)	4.9 (9.51)	5.5 (10.20)	2.8 (8.83)
PR interval (ms)[a]	-0.3 (15.37)	-2.0 (13.37)	-2.6 (15.02)	-1.1 (19.02)	-0.7 (15.07)
QRS duration (ms)	-0.0 (7.53)	0.3 (8.25)	0.5 (9.14)	-0.2 (9.75)	0.4 (8.46)
QT interval (ms)	-2.6 (22.48)	-5.8 (22.53)	-9.9 (22.35)	-11.9 (25.38)	-6.5 (24.24)
QTcF (ms)	-1.3 (17.81)	0.4 (16.41)	-0.9 (16.42)	-1.9 (16.11)	-1.0 (17.98)
QTcB (ms)	-0.5 (20.05)	3.8 (19.21)	3.9 (19.44)	3.5 (18.30)	1.9 (19.91)
Pool S5 (at EOT)	N=545	N=546	N=556	--	N=285
Heart rate (bpm)	0.6 (7.85)	3.5 (9.35)	4.6 (9.62)	--	2.8 (8.83)
PR interval (ms)[b]	-0.3 (16.28)	-1.7 (13.89)	-2.4 (16.05)	--	-0.7 (15.07)
QRS duration (ms)	0.0 (7.09)	0.1 (7.87)	0.8 (8.97)	--	0.4 (8.46)
QT interval (ms)	-2.3 (21.89)	-6.3 (22.10)	-8.9 (22.55)	--	-6.5 (24.24)
QTcF (ms)	-1.2 (17.28)	-0.1 (16.54)	-0.5 (16.61)	--	-1.0 (17.98)
QTcB (ms)	-0.6 (19.72)	3.3 (19.56)	4.0 (19.69)	--	1.9 (19.91)

EOT=end of treatment; Feso=fesoterodine, SD=standard deviation, Tolt=tolterodine

Reviewer's Comment: ***It should be emphasized that increased heart rate is a known pharmacological effect of anti-muscarinic drugs. It is also widely recognized that QTcB overcorrects the QT interval for increased heart rate. Having said that, it should be reiterated that no QT safety signal was identified among patients in either Pool S1 or Pool S5. The average increase in heart rate is small and was clinically tolerated without incident. Nevertheless, this information will be labeled.***

Study SP686 was specifically designed and conducted to assess the effect of fesoterodine at maximum tolerated dose levels on cardiac repolarization compared to placebo and a positive control, moxifloxacin. The study showed that fesoterodine did not affect cardiac repolarization or conduction even at doses as high as 28mg.

III.D.8. Special Safety Concerns

III.D.8.1. Residual Urine/Retention

In the 2 pivotal Phase 3 trials **SP583** and **SP584**, residual urine (in mL) was assessed by

conventional 2-dimensional sonography at each visit except Visit 4 and the safety f/u visit. Modest dose-dependent increases in mean residual volumes were observed in the fesoterodine treatment groups, yet remained well below the 50ml cutoff considered to be clinically relevant.

A total of 18 patients in Pool S1 had residual urine volumes >200ml during the trials, including 1 (<1%) in the placebo group, 3 (<1%) in the fesoterodine 4mg/day group, 10 (1%) in the fesoterodine 8mg/day group, and 4 (2%) in the fesoterodine 12mg/day group. The nine fesoterodine-treated patients from the pivotal trials SP583 and SP584 who had a residual urine volume >200mL are described in Table 12 below.

> ***Reviewer's Comment:*** ***Overall, there were only 9 patients from the two pivotal studies with residual urine >200mL. The majority of those patients (6/9) were female and from fesoterodine 8mg/d group (8/9). In the opinion of this reviewer, increase in the residual volume was generally small and did not pose any problem or require any further medical intervention. Therefore, this is not considered to be a major concern at this time for fesoterodine.***

Table 12.

Fesoterodine-treated subjects with residual urine greater than 200mL (Pool S1)

Subject number	Feso dose (mg/day)	Gender/age	Baseline residual urine (mL)	Residual urine >200mL/visit (mL)	Adverse Event Yes/No
SP583					
11185	8	Female/68	0	228/Visit 3, 238/Visit 5	Yes
SP584					
13096	8	Female/79	0	222/Visit 6	No
13360	8	Female/73	0	221/Visit 3	No
13430	8	Female/81	35	221/Visit 6	Yes[a]
13837	8	Male/69	94	281/Visit 6	Yes[a]
14160	4	Male/80	69	206/Visit 3, 313/Visit 6	Yes[a]
14303	8	Female/73	31	392/Visit 6	Yes[b]
14505	8	Female/66	41	215/Visit 6	No
14799	8	Male/66	90	294/Visit 6	Yes[a]

Feso=fesoterodine

III.D.8.2. Concomitant CYP3A4 Inhibitor Use

Analysis of adverse events in those patients who used CYP3A4 inhibitors during the clinical trials showed that users were more somewhat likely to report an AE from any

system than those who did not use CYP3A4 inhibitors (62% vs 51%, respectively). No particular preferred term appeared to drive the difference in the overall rate. As shown in Table 13 below, the most notable differences between those who used CYP3A4 inhibitors and those who did not were seen with dry mouth (40% vs. 35%, respectively), constipation (9% vs. 5%, respectively), and urinary tract infection (10% vs. 5%, respectively). During open-label treatment dry mouth occurred with similar incidence in patients who did not use CYP3A4 inhibitors, and those who did.

It is notable that a dedicated drug-drug interaction study showed that the administration of 8mg/day of fesoterodine in the presence of ketoconazole 200mg twice daily (a potent inhibitor of CYP3A4) increased C_{max} and AUC of the active hydroxy metabolite (SPM 7605) by 2- 2.5 fold. This increase was more prominent in poor metabolizers of CYP2D6. As a consequence, the maximum recommended dose of fesoterodine in patients taking strong inhibitors of CYP3A4 will be 4mg.

Table 13.

Adverse events reported by ≥10% of subjects in any fesoterodine treatment group who used CYP3A4 inhibitors and that occurred more often than those who did not use CYP3A4 inhibitors (Pool S1)

Preferred term	CYP3A4 inhibitor use	Placebo N=780 n (%)	Feso 4mg/day N=782 n (%)	Feso 8mg/day N=785 n (%)	Feso 12mg/day N=222 n (%)	Tolt 4mg/day N=290 n (%)
CYP3A4 inhibitor use	**Yes**	**218**	**193**	**212**	**40**	**73**
	No	**562**	**589**	**573**	**182**	**217**
Dry mouth	Yes	16 (7)	48 (25)	92 (43)	20 (50)	17 (23)
	No	49 (9)	125 (21)	183 (32)	93 (51)	32 (15)
Constipation	Yes	3 (1)	10 (5)	18 (9)	4 (10)	2 (3)
	No	16 (3)	18 (3)	29 (5)	14 (8)	6 (3)
Urinary tract infection	Yes	7 (3)	5 (3)	12 (6)	4 (10)	3 (4)
	No	15 (3)	21 (4)	20 (4)	1 (<1)	1 (<1)
Dry throat	Yes	3 (1)	4 (2)	9 (4)	5 (13)	1 (1)
	No	1 (<1)	4 (<1)	8 (1)	9 (5)	2 (<1)
Nausea	Yes	4 (2)	2 (1)	5 (2)	4 (10)	1 (1)
	No	20 (4)	15 (3)	13 (2)	11 (6)	5 (2)

Feso=fesoterodine, Tolt=tolterodine

III.D.8.3. Use with Other Medications

Compared with the overall AE profile for fesoterodine, there were no specific trends pointing to an increase in adverse events in any patient group taking any specific concomitant drug (other than CYP3A4 inhibitors).

The following items were notable, but did not constitute major safety concerns:

-Patients taking drugs for acid related disorders were more likely to report dyspepsia, abdominal pain upper, and dry mouth than those who did not take drugs for acid-related disorders, but overall patient numbers were low.

-Patients taking antibacterials for systemic use were more likely to report lacrimal disorder (dry eye) and dry mouth than those who did not take systemic antibacterials. Urinary tract infection, upper respiratory tract infection, influenza, and cough also were reported at higher rates in patients taking antibacterials as these conditions were probably the reasons for taking antibacterials.

-Patients taking vitamins and mineral supplements had slightly higher rates of dry mouth and constipation in the fesoterodine 8mg/day group compared to the overall adverse event rates, but the rates of dry mouth were also higher for placebo in this patient group.

-Patients taking beta blocking agents were more likely to report asthenia in the fesoterodine 12mg/day group than other patients, but the patient numbers were very low. No specific cardiovascular events were reported in this specific situation.

-Patients taking calcium channel blockers were more likely to report dry mouth but no specific cardiovascular adverse events were seen in this situation.

-Diuretics did not appear to influence the overall AE profile, but in the fesoterodine 4mg/day group, patients taking diuretics were more likely to report an AE from any system organ class (52%) than those not taking diuretics (42%), though no particular preferred term seemed to drive this difference in the overall AE rate. Specifically, rates of dry mouth and constipation were similar in those taking diuretics to those not taking them.

-Serum lipid reducing agents did not appear to influence the AE profile, but in the fesoterodine 8mg/day group, patients taking serum lipid reducing agents were more likely to report an AE from any system organ class (57%), than those not taking serum lipid reducing agents (47%). This difference was also seen in the dry mouth rate in the fesoterodine 8mg/day group, where 45% of patients taking serum lipid reducing agents reported dry mouth, compared with 33% of patients who did not take this class of medication.

-Patients taking anti-inflammatory and antirheumatic products were more likely to report dry mouth, especially in the fesoterodine 8 and 12mg/day groups.

-Patients taking analgesics were more likely to report dry mouth and a slight increase in the constipation rates with the fesoterodine 8 and 12mg/day doses.

-Patients taking neuroleptics were more likely to report dry mouth in the fesoterodine treatment groups but had no increased rates of nervous system related adverse events.

-Patients taking antihistamines for systemic use were more likely to report a slightly higher dry mouth rate with the fesoterodine 8mg dose than those who did not take antihistamines, but no increase in nervous system adverse events was reported. Overall, patient numbers were low.

III.D.8.4. Use in pregnancy and lactation

There are no adequate and well-controlled trials or data using fesoterodine in pregnant women. At exposures higher than those observed at the to-be-marketed doses, there was evidence of an effect of fesoterodine on fetal development. Taken together, this information supports labeling as a Category C drug, to be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

It is not known at this time, whether fesoterodine is excreted in human milk. Therefore, fesoterodine should not be administered during nursing.

III.D.8.4. Overdose

Overdosage with antimuscarinic agents such as fesoterodine can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended. Fesoterodine has been safely administered in clinical trials at doses up to 28mg/day.

III.D.8.5. Effects on ability to drive or operate machinery

No trials on the effects on the ability to drive and use machines have been performed. As with other antimuscarinic agents, caution should be exercised by individual patients when driving or using machines until the effects of fesoterodine are known to them. This is due to possible occurrence of undesirable effects. It provides some comfort that dizziness (placebo: 2%, fesoterodine 4mg/day: 2%, fesoterodine 8mg/day: 1%), blurred vision (1%, <1%, <1%), and somnolence (<1%, <1%, <1%), were observed at the same or lower rates in fesoterodine-treated patients compared to placebo-treated patients in Phase 2 and 3 trials.

III.D.9. Anticholinergic Side Effects

The most common antimuscarinic adverse events associated with fesoterodine use were dry mouth, constipation, UTI, urinary retention and dry eyes. None of these required significant medical intervention at any point during the two pivotal trials.

Patients who developed urinary retention, although a recognized adverse event of anticholinergics, were found to be mild in intensity. None of these patients required hospitalization or any serious medical intervention and all patients had full recovery.

III.E. Safety Summary

To reiterate, the most common overall adverse events associated with fesoterodine were related to its antimuscurinic effect. The most common antimuscarinic adverse events associated with fesoterodine were: dry mouth, constipation, UTI, urinary retention and dry eyes. None of these required significant medical intervention at any point during the

two pivotal trials. Adverse events in the open-label extension studies were consistent with those reported in the shorter-term pivotal trials.

Poor metabolizers of CYP2D6 were more likely than extensive metabolizers to experience AE's, particularly those known to be associated with antimuscarinic treatment. This effect was more pronounced in the fesoterodine 8mg/day group, and included: constipation, dry mouth, dry eye, and dyspepsia.

There were some differences in AE patterns based on age, with constipation, urinary tract infection and dizziness occurring more often in older (≥65 years and ≥75 years) patients. Headache was more common in younger patients.

Gender appeared to play a role in the frequency of some AEs including dry mouth which occurred more often in females than in males, but overall there was no indication of an effect by gender on the AE profile. Race did not appear to influence the AE profile. Concomitant diseases had little effect on the AE profile.

Mean residual urine volume was increased by fesoterodine, but in large part, this effect was not considered to be large enough to reflect significant risk. Small dose-dependent increases in residual volume were seen in both sexes; however this increase was more pronounced in men. In addition, age seemed to be a factor. Increases in mean residual urine volume were larger in patients ≥75 years of age, as compared to younger patients, but there was no noteworthy difference between patients ≥65 and those <65 (15mL and 14mL).

Mean changes from baseline in vital signs showed a mild increase in heart rate. Changes in vital signs by age group were generally similar to those in the overall population in both Pool S1 and Pool S5. Mean changes from baseline in ECG results; again, noted to show a fesoterodine-related increase in heart rate, were generally similar between patients <65 and ≥65 years of age. Among patients on fesoterodine, there was no evidence that ECG results in patients ≥75 years of age differed from results among younger patients in a clinically relevant way. Gender and CYP2D6 metabolizer status did not impact on the fesoterodine-related changes in heart rate.

In regard to potential effect on the QT interval, no male or female patient ≥65 years of age treated with fesoterodine had a QTcF or QTcB ≥500ms. One female patient <65 years of age had a ≥60ms increase from baseline in QTcB.

III.F. Safety Conclusions

1. **The data submitted in this application supports the overall safety of fesoterodine at doses of 4mg and 8mg once daily in patients with OAB. Based upon its known antimuscurinic class side effects (e.g. dry mouth, constipation, urinary retention, and increase in heart rate), it should be used with caution in certain patient populations, including:**
    - **Patients with history of pre-existing ileus or intestinal obstruction.**
    - **Patients with bladder outlet obstruction.**
    - **Patients with glaucoma.**

2. **Fesoterodine may cause constipation and urinary retention in susceptible patients and should be discontinued in patients who report prolonged constipation or urinary retention unrelieved by temporary cessation of medication.**

3. **Dose should be limited to 4mg in certain patient populations, including:**
    - **Patients with severe renal insufficiency (CLcr<30mL/min).**
    - **Patients taking strong inhibitors of CYP3A4.**

4. **Fesoterodine should be used during pregnancy only where the benefits are believed to outweigh the potential risks to fetus as demonstrated in preclinical studies.**

APPENDIX – A

Medical Officer's Review of Fesoterodine Phase 3 Study Report (SP584)

NDA 22-030

Date of Submission:	**March 27, 2006**
NDA Goal Date:	**January 27, 2007**
Action Date:	**January 26, 2007**
Sponsor:	**Schwarz Biosciences, Inc.**
Drug Name:	
Referred Name:	**SPM 8272, Fesoterodine**
Proposed Trade Name:	**[redacted]** b(4)
Pharmacologic Category:	**Anti-Cholinergic (Muscarinic Receptor Antagonist)**
Study Number:	**SP584**
Development Phase:	**3**
Trial Initiation Date:	**October 30, 2003**
Trial Completion Date:	**February 10, 2005**
Indication:	**Treatment of Overactive Bladder (OAB)**
Doses Used:	**4mg & 8mg once a day**
Route of Administration	**Oral**

Background:

Therapy for OAB focuses on symptomatic treatment since the underlying cause for the condition is not known in most non-neurogenic cases. The basic treatments for OAB are either non-drug treatment such as behavioral training, use of incontinence pads or other protective equipment, sacral nerve stimulation, or the use of anti-muscarinic drugs These drugs antagonize the acetylcholine-induced stimulation of postganglionic muscarinic receptors. Muscarinic receptors are thought to mediate not only the detrusor contractions of normal voiding but also the involuntary contractions in OAB that are associated with urge and urge incontinence.

Overactive bladder affects at least 10% of the overall adult population. The prevalence of detrusor overactivity increases with age, and 40% of all individuals over the age of 50 have some form of detrusor overactivity, rising to 60% - 80% in institutionalized patients. The majority of patients are women.

During the development of fesoterodine fumarate, Phase 2 dose-finding trials were conducted to evaluate the tolerability, safety, and efficacy of 4, 8, and 12mg administered once daily. From these investigations, it was determined that 4 and 8mg/day were the optimal doses of the SR formulation to use for this Phase 3 trial (**SP584**).

Study Design:
This was a randomized, double-blind, placebo-controlled, multi-center trial to study the efficacy, tolerability, and safety of fesoterodine in male and female adult patients with OAB. After eligibility was confirmed, patients entered a 2-week Run-In period during which all patients received 1 placebo tablet each morning. Following this Run-In period, eligible patients were randomized to 1 of 3 treatment arms and received either placebo, fesoterodine 4mg/day, or fesoterodine 8mg/day for 12 weeks during the double-blind treatment period. Trial medication was taken orally once daily in the morning with or without food. Patients who did not enroll in the follow-up, open-label extension study (SP739) attended a final follow-up Safety visit approximately 2 weeks after the treatment period ended.

Tabular Schedule for Visits:
V1 = Start of 2 week placebo Run-in Period
V2 = Randomization to one of the three treatment arms and start of 12-week treatment period
V3 = Safety and compliance visit after 2 weeks of treatment
V4 = Safety and compliance visit after 4 weeks of treatment
V5 = Safety and compliance visit after 8 weeks of treatment
V6 = End of 12-week Treatment period and termination visit
FU = Safety Follow-up visit 2 weeks after end of Treatment Period

The eligible patients were randomized to 1 of the following 3 treatment arms:
Appendix A. Table 1. Treatment Arms

Number of treatment arms:	Three arms, parallel-group: fesoterodine 4mg/day, fesoterodine 8mg/day, or placebo
Trial medication:	Treatment Arm 1: 1 placebo tablet Treatment Arm 2: 1 fesoterodine fumarate (SR) 4mg tablet Treatment Arm 3: 1 fesoterodine fumarate (SR) 8mg tablet

The planned duration of the trial per patient was approximately 16 weeks which is divided into the following periods:
Appendix A. Table 2. Treatment Periods

Run-In (pre-treatment) Period:	2 weeks
Treatment Period:	12 weeks
Safety Follow-Up Period:	2 weeks

After successful completion of Visit 2, patients were consecutively randomized to 1 of the 3 treatment arms (1, 2, or 3). Patients were assigned randomization numbers by IVRS according to a computer-generated randomization schedule, which served as the basis for packaging of the trial medication.

Eligible patients received either placebo, or fesoterodine SR 4mg/day or 8mg/day. The doses of fesoterodine SR used in this trial were shown to be safe and well tolerated in previous Phase 1 trials and Phase 2 dose-ranging trials. The dosages tested in the two Phase 2 dose-finding trials **(SP668 and SP582)** were 4, 8, and 12mg/day of fesoterodine SR. Based on the results of the Phase 2 trials, including over 900 patients, the doses of 4 and 8mg/day were chosen for further development.

Patients were instructed to take fesoterodine tablets once daily in the morning, either with or without food. Placebo was used and considered as an appropriate control and the trial was designed with a 2-week Placebo Run-In Period. The Placebo Run-In Period was useful to determine which patients would be able to thoroughly complete the micturition diaries (since 2 of the 3 primary efficacy variables were dependent on accurate recording of this information).

Patients were asked to complete a 3-day micturition diary for 4 periods during the course of the trial (i.e., for 3 consecutive days during the week immediately prior to Visits 2, 3, 5, and 6). The diary captured the time from when a patient woke up in the morning to actively start the day, to when a patient went to bed in the evening and each time the patient went to the toilet. Patients were also to record information on each micturition and episode of incontinence. During Day 1 of these 3 consecutive days, patients measured their voided volume (ml) using the urine cup provided.

Population PK analysis was done in this trial. Sampling at Visit 2, 3, 5 and 6 matched the timing of certain pharmacodynamic measurements (i.e., measurement of residual urine, ECG measurements). The analysis aimed to characterize the inter- and intra-individual variability of the PK parameters of SPM 7605 in the trial population. Another objective of the analysis was to quantify the relationship between different patient specific factors such as age, sex, body mass index (BMI), metabolization status for CYP2D6, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, creatinine clearance, total bilirubin, and the PK model parameters.

Data on the CYP 2D6 metabolizer status of these patients was collected because differentiating between poor and extensive metabolizers for CYP2D6 provides further information about the efficacy and safety of fesoterodine, particularly in poor metabolizers. It is known that approximately 7% to 10% of Caucasians are "poor metabolizers" for CYP2D6.

Inclusion Criteria:
The following inclusion criteria had to be met before randomization:

- Patients with signs and symptoms of OAB (increased urinary frequency, urinary urgency, with or without incontinence) for at least 6 months before enrollment. Of note: A protocol amendment was made to revise this criterion to add that patients with urinary urge incontinence must have had it for at least 1 month before enrollment.
- Patients with at least 8 micturitions per 24 hours.

- Patient is at least 18 years of age.
- Women of child-bearing potential to use contraception (eg, barrier method, hormonal) and have a negative pregnancy test.
- Patients were required to complete the diary in a legible and plausible manner for all 3 consecutive days during the 7 days prior to Visit 2.
- Patients with a total of at least 6 urinary urgency episodes or at least 3 urinary urge incontinence episodes documented during the 3-day diary period.
- Patients have at least 8 micturitions per 24 hours confirmed on each day of the 3-day diary period.
- Patients have documented the voided volume for 1 complete day during the 3-day diary period.
- Patient has indicated, based on the Likert scale, that his/her condition causes him/her at least "moderate problems".

Exclusion Criteria:

A subject could not enroll in the trial if the following criteria were present:

- Patient has previously been randomized in any trial using this investigational compound or in another trial of an investigational drug within the last 30 days.
- Patient has history of chronic alcohol or drug abuse within the last 6 months.
- Patient has any known medical or psychiatric condition, which in the opinion of the investigator would compromise the patient's ability to participate in this trial (eg, progressive malignant disease, human immunodeficiency virus infection, progressive or mental disability, major surgery within the last 4 weeks).
- Patient has known hypersensitivity to any components of the trial medication as stated in the protocol.
- Patient is a pregnant or lactating woman.
- Patient has a known neurological disease influencing bladder function (e.g., multiple sclerosis, Parkinson's disease, spinal cord injuries, spina bifida, autonomic neuropathy).
- Patient has a known lower urinary tract pathology in the investigator's opinion potentially responsible for urge or incontinence (e.g., bladder stone, interstitial cystitis, urothelial tumors or stress incontinence).
- Patient has an active urinary tract infection as shown by the results of the urinalysis at visit 1 or documented recurrent urinary tract infections (>2 per year).
- Patient is known to have clinically relevant bladder outlet obstruction.
- Patient has a residual urine volume >100mL.
- Patient is known to have polyuria (>3000mL/24h).
- Patient is known to have increased frequency and/or nocturia due to renal insufficiency or heart failure.
- Patient is known to have obstructive disease of the gastrointestinal tract, inflammatory bowel disease, megacolon (including toxic), intestinal atony, or paralytic ileus.
- Patient is known to have myasthenia gravis.

- Patient has clinically relevant arrhythmia and/or unstable angina pectoris and/or other unstable cardiovascular conditions, or pacemaker in place as known from medical history or as shown by the ECG at Visit 1.
- Patient has a QTcB interval of >500ms as shown by the ECG.
- Patient is known to have angle-closure glaucoma or narrow anterior chamber angles.
- Patient has been treated with drugs with antimuscarinic properties indicated for treatment of OAB such as tolterodine, oxybutynin, trospium chloride, propiverin, flavoxate, hyoscyamine, or any other medication which is indicated for the treatment of OAB.
- Patient actively uses amantadine, class Ia (eg, quinidine) and class III (eg, amiodarone) antiarrhythmic drugs.
- Patient has started treatment with tricyclic antidepressants, neuroleptics, or estrogen replacement therapy within 4 weeks prior to Visit 1.
- Patient has sèvere renal and/or hepatic diseases as known from medical history.

Reviewer's Comment: Although fairly strict, both inclusion and exclusion criteria are appropriate and acceptable.

A patient could not be randomized if the following discontinuation criteria were met at Baseline:

1. Patient has an incomplete diary for the Run-In period, on any 1 of the 3 days or the voided volume is missing.
2. Patient has a residual urine volume >100mL.
3. Patient has polyuria (>3000mL/24h) or a voided volume >500mL for any micturition during the Run-In period.
4. Patient has creatinine ≥1.6mg/dL (≥142µmol/L); total bilirubin ≥1.5mg/dL (≥26µmol/L); ALT, AST, or GGT ≥2 x upper normal range as confirmed by the blood test performed at Visit 1 (mention of blood test added via Protocol Amendment 1).
5. Patient has clinically relevant out-of-range values for hematology or serum chemistry as confirmed by the blood test performed at Visit 1 or out of range urinalysis parameters as confirmed by the urinalysis at Visit 2.

Efficacy Evaluations:

Primary Efficacy Endpoint:
The primary efficacy endpoints for this trial were:

- "Change in number of micturitions (frequency) per 24 hours" (from baseline to after 12 weeks of treatment).
- "Change in number of urge incontinence episodes per 24 hours" (from baseline to after 12 weeks of treatment).

Key Secondary Efficacy Endpoint:
A key seconday efficacy endpoint was change in volume voided per micturition (from baseline to after 12 weeks pf treatment)..

Reviewer's Comment: ***The co-primary endpoints and key secondary endpoint selected for this study were appropriate to support the OAB indications and are consistent with the Division's expectations.***

Safety Evaluations:
Safety and tolerability assessments included the monitoring of clinical adverse events, vital signs, routine laboratories (chemistry, hematology and urinalysis) and physical examinations.

Extent of Exposure:
Planned treatment duration for randomized patients was 84 days with an allowable protocol deviation of ±3 days, resulting in up to 87 days of treatment. The extent of exposure demonstrated that the double-blind trial design was well-maintained during the trial. The mean exposure to trial medication was similar across treatment groups: placebo: 78 days, fesoterodine 4mg/day: 74 days, fesoterodine 8mg/day: 76 days. Over 80% of patients in each group were exposed to trial drug for at least 71 days.

Safety Results:

Overall Adverse Events:
Treatment-emergent adverse events (TEAEs) were reported for 149/271 (55%) of patients in the placebo group, 171/282 (61%) of patients in the fesoterodine 4mg/day group and 193/279 (69%) of patients in the fesoterodine 8mg/day group. The following table shows all TEAE's reported with an incidence of at least 2% during the overall treatment period.

Appendix A. Table 3. Summary of TEAEs reported by >2% of patients in at least 1 treatment group.

Preferred term	Placebo N=271 n (%)	Feso 4mg/day N=282 n (%)	Feso 8mg/day N=279 n (%)
Dry mouth	19 (7)	45 (16)	99 (36)
Constipation	7 (3)	14 (5)	21 (8)
Urinary tract infection	11 (4)	10 (4)	15 (5)
Upper respiratory tract infection	7 (3)	12 (4)	9 (3)
Keratoconjunctivitis sicca (dry eyes)	0	2 (1)	9 (3)
Headache	9 (3)	12 (4)	8 (3)
Nausea	6 (2)	3 (1)	7 (3)
Diarrhea	8 (3)	7 (3)	6 (2)
Urinary retention	1 (<1)	4 (1)	6 (2)
Sinusitis	6 (2)	3 (1)	6 (2)
Cough	3 (1)	6 (2)	4 (1)
Nasopharyngitis	7 (3)	10 (4)	2 (1)
Back pain	1 (<1)	7 (3)	2 (1)
Hypertension	6 (2)	7 (3)	0

Adverse events that were reported more commonly in patients treated with either dose of fesoterodine than in placebo included (in descending order of frequency for fesoterodine 8mg/day): dry mouth, constipation, urinary tract infection, upper respiratory tract infection, keratoconjunctivitis sicca (dry eyes), headache, nausea, urinary retention, cough, nasopharyngitis, back pain, and hypertension.

Of these, dry mouth, constipation, urinary tract infection, dry eyes, nausea, and urinary retention were more common at 8mg/day than at 4mg/day.

Among the small number of poor metabolizers receiving fesoterodine during this trial, the AE profile was not substantially different from the total population, although dry mouth was somewhat more common in these patients than in the overall population (placebo=10%, fesoterodine 4mg/day=25%, fesoterodine 8mg/day=48%).

The following table shows TEAE's for each treatment group by intensity and by maximum intensity.

Appendix A. Table 4. Summary of treatment-emergent adverse events by intensity

AE Intensity	Placebo N=271	Feso 4mg/day N=282	Feso 8mg/day N=279
By intensity n (%) [number of AEs]			
Mild	105 (39) [179]	121 (43) [210]	138 (50) [244]
Moderate	63 (23) [88]	85 (30) [135]	96 (34) [163]
Severe	11 (4) [18]	16 (6) [23]	22 (8) [27]
By maximum intensity n (%)			
Mild	80 (30)	83 (29)	90 (32)
Moderate	58 (21)	72 (26)	81 (29)
Severe	11 (4)	16 (6)	22 (8)

AE=adverse event, Feso=fesoterodine, SS=safety set

Most AE's were mild in intensity. The incidence of patients reporting events of severe intensity was low and similar for the different treatment groups.

The following table shows TEAE's considered be at least possibly related to trial medication by the investigator for each treatment group.

Appendix A. Table 5. Summary of patient's with treatment-emergent adverse events considered at least possibly related to trial medication and reported by ≥2% of patients in at least 1 treatment group.

Preferred term	Placebo N=271 n (%)	Feso 4mg/day N=282 n (%)	Feso 8mg/day N=279 n (%)
Dry mouth	19 (7)	45 (16)	97 (35)
Constipation	7 (3)	14 (5)	18 (7)
Keratoconjunctivitis sicca (dry eyes)	0	2 (1)	9 (3)
Headache	7 (3)	7 (3)	6 (2)

Feso=fesoterodine, SS=safety set

The most common AE's considered to be related to trial medication by the investigators are consistent with those reported with drugs in the anti-muscurinic class: dry mouth, constipation and dry eyes. Headache was considered to be related to trial medication in similar numbers of placebo- and fesoterodine-treated patients.

The following table shows TEAE's by CYP2D6 metabolizer status for each treatment group.

Appendix A. Table 6. Summary of patients with treatment-emergent adverse events reported during the double-blind treatment period by metabolizer status.

	Placebo	Feso 4mg/day	Feso 8mg/day
By metabolization status			
Poor metabolizers	N=30	N=28	N=21
	19 (63)	17 (61)	12 (57)
Extensive metabolizers	N=235	N=252	N=253
	121 (52)	151 (60)	170 (67)

Feso=fesoterodine, SS=safety set

Metabolizer status did not seem to have an impact on the overall incidence of AE's as seen in the table above. In addition, poor and extensive metabolizers had similar rates of AE's considered by the investigator to be related to trial medication.

A summary of CYP2D6 poor metabolizers with treatment-emergent adverse events reported by >2 patients in either fesoterodine treatment group during the double-blind treatment period is provided in the following table.

Appendix A. Table 7. Summary of CYP2D6 poor metabolizers with treatment-emergent adverse events reported by >2 patients in the fesoterodine 4mg or 8mg/day group.

Preferred term	Placebo N=30 n (%)	Feso 4mg/day N=28 n (%)	Feso 8mg/day N=21 n (%)
Dry mouth	3 (10)	7 (25)	10 (48)
Keratoconjunctivitis sicca (dry eyes)	0	0	3 (14)
Constipation	0	2 (7)	1 (5)
Arthralgia	3 (10)	0	1 (5)
Diarrhea	1 (3)	3 (11)	0

Feso=fesoterodine, SS=safety set

The AE profile of CYP2D6 poor metabolizers during the double-blind treatment period was generally similar to that in the overall population. Dry mouth and dry eyes were reported in higher percentages of poor metabolizers as compared to the population as a whole. Further interpretation of these results is limited due to the small number of patients in this subgroup.

> ***Reviewer's Comment:*** ***This clinical reviewer concurs with the sponsor's analysis that the adverse event profile of CYP2D6 poor metabolizers is consistent with and similar to the overall population. However, it should be recognized that dry mouth and dry eyes are key adverse events that are seen irrespective of metabolization status with anti-muscarinic drugs as a class.***

The following table shows TEAE's by age group for each treatment group.

Appendix A. Table 8. TEAE's presented by age group.

Subgroup	Placebo n (%)	Feso 4mg/day n (%)	Feso 8mg/day n (%)
By age group			
<65 years old	N=180 90 (50)	N=186 116 (62)	N=182 112 (62)
≥65 years old	N=91 52 (57)	N=96 52 (54)	N=97 75 (77)

Overall AE rates during the double-blind treatment period were not substantially different between patients <65 and ≥65 years of age treated with placebo or fesoterodine 4mg/day. However, patients ≥65 years of age treated with fesoterodine 8mg/day had more AE's than younger patients (77% vs 62%) mainly as a result of dry mouth and constipation rates. A summary of patients ≥65 years of age with those treatment-emergent adverse events reported by >2 patients in either fesoterodine treatment group during the double-blind treatment period is presented in the following table.

Appendix A. Table 9. Summary of patients ≥65 years of age with treatment-emergent adverse events reported by >2 patients in the fesoterodine 4mg or 8mg/day group.

Preferred term	Placebo N=91 n (%)	Feso 4mg/day N=96 n (%)	Feso 8mg/day N=97 n (%)
Dry mouth	7 (8)	14 (15)	39 (40)
Constipation	2 (2)	4 (4)	15 (16)
Urinary tract infection	6 (7)	4 (4)	7 (7)
Urinary retention	1 (1)	2 (2)	4 (4)
Keratoconjunctivitis sicca (dry eyes)	0	0	4 (4)
Flatulence	1 (1)	0	3 (3)
Hypertension	3 (3)	5 (5)	0
Nasopharyngitis	1 (1)	4 (4)	0
Blood creatine phosphokinase increased	1 (1)	3 (3)	0

Feso=fesoterodine, SS=safety set

The AE profile of patients ≥65 years of age during this trial was generally similar to that in overall population both in distribution of events and incidence. Dry mouth was reported for 40% of patients ≥65 years of age taking fesoterodine 8mg/day compared to 33% of patients <65 years of age at those doses. Constipation was reported for 16% of

patients ≥65 years of age taking fesoterodine 8mg/day compared to 3% of patients <65 years of age at this dose.

> ***Reviewer's Comment:*** ***The clinical impression of this reviewer is that the adverse event profile is similar in distribution for patients below age 65 years and above age 65 years. However, the frequency for dry mouth and constipation are higher in the age group of >65 years as is expected with all anti-cholinergic/anti-muscarinic drugs in this class. Both these adverse events were seen more commonly in patients taking fesoterodine 8 mg/day.***

Overall TEAEs Reported During the Safety Follow-Up Period
During the 30-day Safety Follow-Up Period, treatment-emergent adverse were reported for 8/114 (7%) of patients in the placebo group, 10/118 (9%) of patients in the fesoterodine 4mg/day group, and 16/127 (13%) of patients in the fesoterodine 8mg/day group. These adverse events occurred across multiple system organ classes with no obvious grouping or trends.

Deaths:
There were no deaths reported in this trial.

However, as per a recent adverse event report submitted by the sponsor on October 25, 2006, there was one adverse event of death reported in a 76 year old female who received fesoterodine during **SP739**, an open label extension trial for the treatment of OAB for patients completing **SP584.** The patient had been on fesoterodine for at least fifteen plus months before the event occurred and received concomitant medications for co-morbid medical conditions. This event of death was determined to be unrelated to the study medication by the investigator. Cause of death was listed as "natural causes".

> ***Reviewer's Comment:*** ***From the brief adverse event report submitted by the sponsor, this clinical reviewer concurs with the investigator.***

Serious Adverse Events:
A total of 2% - 3% of patients in each treatment group had a serious adverse event reported during this trial. Serious AE's reported for patients receiving fesoterodine included: cataract, colitis, chest pain, pneumonia, gastroenteritis viral, sinusitis, appendicitis, clostridial infection, ankle fracture, postoperative respiratory distress, abnormal liver function tests, arthralgia, brain neoplasm, malignant melanoma, pneumomediastinum, knee arthroplasty, rotator cuff repair, spinal decompression, and thoracotomy.

"Spinal decompression" was the only SAE reported by a poor metabolizer receiving fesoterodine (4mg/day group). In the opinion of the investigator, this AE was not related to trial medication.

Reviewer's Comment: ***After reviewing the details of this case report, this clinical reviewer agrees with the investigator that fesoterodine is not related to the causation of spinal decompression as there were other more serious co-existing disease conditions that could have contributed to this event in this patient.***

Of the 21 patients with SAE's, only 1 patient (in the placebo group) experienced a SAE (atrial fibrillation) considered by the investigator to be related to trial medication. The remaining SAE's in placebo-treated patients and all SAE's in fesoterodine-treated patients were considered by the investigator to either have an unlikely relationship to trial medication or were considered by the investigator to be unrelated to trial medication.

One placebo-treated patient who had pneumonia and 3 fesoterodine-treated patients discontinued from the trial as a result of SAE's. None of these AE's resulting in discontinuation from the trial was considered by the investigator to be related to trial medication. Information on the fesoterodine cases is outlined in the following table.

Appendix A. Table 10. Patients with treatment-emergent SAE's that resulted in discontinuation from fesoterodine treatment.

Subject #/ metabolization status/ gender/ age	Relative day[a]/ dose at AE onset	Serious adverse event (preferred term/ reported term)	Intensity/ relationship/ outcome
14583/ EM/ female/ 68	Day 36/ fesoterodine 4mg/day	Ankle fracture/ broke left ankle	Moderate/ unlikely/ recovered/resolved
14776/ EM/ male/ 62	Day 67/ fesoterodine 4mg/day	Lung disorder/ wedge resection of left lung lesion Thoracotomy/ thoracotomy	Severe/ not related/ recovered/resolved (both events)
13809/ PM/ female/ 46	Day 65/ fesoterodine 4mg/day	Spinal decompression/ Decompression L4-5	Moderate/ not related/ recovered/resolved

AE=adverse event, EM=extensive metabolizer, L=lumbar, PM=poor metabolizer, SS=safety set

Discontinuation Due to Adverse Events:
A total of 53 patients discontinued due to AE's during treatment: 11/271 patients (4%) in the placebo group, 17/282 patients (6%) in the fesoterodine 4mg/day group, and 25/279 patients (9%) in the fesoterodine 8mg/day group.

Dry mouth, urinary retention, increased GGT, constipation, and headache resulted in discontinuation more often in fesoterodine-treated patients than in placebo-treated patients.

Adverse events that resulted in discontinuation in >1% of patients in any treatment group

Included: dry mouth (1.1% in fesoterodine 4mg/day, 1.8% in fesoterodine 8mg/day) and urinary retention (1.1% in fesoterodine 8mg/day).

Rate of discontinuation due to AE's in patients treated with placebo, fesoterodine 4mg/day and fesoterodine 8mg/day were 3%, 11%, and 5% respectively, among poor metabolizers, and 4%, 6%, and 8%, respectively, among extensive metabolizers. No individual AE resulted in discontinuation of more than 1 poor metabolizer from the trial.

A total of three patients (all taking fesoterodine 4mg/day) were discontinued due to SAE's. (patient with ankle fracture, patient s/p thoracotomy and patient with spinal decompression, as described above).

Other Adverse Events Of Special Interest:
Adverse events that are typically noted after treatment with anti-muscarinic agents include: **dry mouth, constipation, dry eyes, urinary retention and tachycardia.** Therefore, the incidence of these events reported as AE's was reviewed in greater detail, as follows:

Dry Mouth
Dry mouth was reported in 7% of patients treated with placebo, 16% of patients treated with fesoterodine 4mg/day, and 36% of patients treated with fesoterodine 8mg/day. Time to first occurrence of dry mouth for patients taking fesoterodine was generally within the first month of treatment. Although many patients treated with fesoterodine had dry mouth, the event was usually mild to moderate in intensity. None of these events was considered to be serious. Discontinuation from trial medication as a result of dry mouth was low. About 1% (8/561) of all fesoterodine-treated patients dropped out as a result of dry mouth (1.1% in fesoterodine 4mg/day, 1.8% in fesoterodine 8mg/day and 1.4% overall).

In one case (**Patient # 13211** on fesoterodine 8mg/day) the trial medication was withdrawn and the patient discontinued the trial as a result of this AE.

Incidence of dry mouth was similar in patients less than 65 years and those ≥65 years of age. Dry mouth was somewhat more common in CYP2D6 poor metabolizer patients than in the overall population (for poor metabolizers: placebo=10%, fesoterodine 4mg/day=25% and fesoterodine 8mg/day=48%) However, poor metabolizers did not appear to have more severe dry mouth compared to extensive metabolizers.

> ***Reviewer's Comment: According to this clinical reviewer, there is no unusual increase in the number of patients reporting dry mouth from this study. Those who reported dry mouth experienced mild to moderate dryness and no one required any special medical intervention. Dry mouth is a known adverse event associated with the use of anti-muscarinic medications.***

Urinary Retention:
Urinary retention was reported as an AE in 1/271 (<1%) of patients treated with placebo, 4/282 (1%) of patients treated with fesoterodine 4mg/day, and 6/279 (2%) of patients treated with fesoterodine 8mg/day. All cases of urinary retention were mild or moderate in severity. None of these adverse events was considered serious. Discontinuation from trial medication as a result of urinary retention was low [about 1% (5/561)] amongst the fesoterodine-treated patients. For a clearer picture of this AE, a few case narratives are provided herein:

Patient # 14303 a 73-year-old female, poor metabolizer, had an AE of moderate "residual urine volume" starting at Day 14 of treatment with fesoterodine 8mg/day. Her residual urine volumes were 31mL at baseline and 392mL at Visit 6. Trial medication was withdrawn and the patient discontinued from the trial due to residual urinary retention. The event did not require any further medical intervention such as catheterization.

Patient #14160 was an 80-year-old Caucasian male. His medical history included multiple co-morbidities. He entered the trial on 27 April 2004 with the diagnosis of overactive bladder. The patient was randomized to fesoterodine 4mg/day on 10 May 2004. At the time of the AE, the patient was taking fesoterodine 4mg/day and had been at this dose level for 14 days. On 24 May 2004 at Visit 3, the patient developed "urinary retention" (residual urine of 206mL). No therapeutic measures were taken other than discontinuing the trial medication. The intensity of the AE was rated to be moderate. The patient had recovered from the urinary retention by 07 Jun 2004 at Visit 6 (residula urine of 31mL).

Patient # 13940 was a 66-year-old Caucasian male. His medical history in addition to other co-morbid conditions included BPH. The patient was randomized to fesoterodine 8mg/day. At the time of the SAE, the patient was taking fesoterodine 8mg/day and had been at this dose level for 2 days. Four days later, the patient complained of difficulty emptying his bladder. The intensity of the AE was rated to be moderate. The patient recovered from the event 3 days after the first symptom. At all visits there was no residual urine detected. The patient withdrew consent from the trial due to the sensation of difficulty emptying his bladder. Trial medication was discontinued on 11 Apr 2004 and the subject recovered from the adverse event on the same day. Due to the timing and the positive response on withdrawal, the sponsor assessed the event as probably related to trial medication.

Patient # 13430 was an 81-year-old Caucasian female. Her medical history included significant medical co-morbidities. She entered the trial with the diagnosis of overactive bladder. At the time of the reported adverse event, the patient was taking fesoterodine 8mg/day and had been at this dose level for 14 days. Approximately 2 weeks after blinded trial medication was started, her post void residual urine measurement was 221mL (baseline residual was 35mL). The patient attempted to void again. She was unable to empty her bladder completely. Final residual urine measurement was 336mL. The intensity of the AE was rated to be mild. The patient was withdrawn from the trial due to the even. The urinary retention was not classified as a serious adverse event. The

investigator and sponsor assessed the relationship of urinary retention to trial medication as probably related.

> ***Reviewer's Comment:*** ***This clinical reviewer acknowledges that urinary retention and increased residual urine are known to be associated with anti-cholinergic medication and the narratives of all four cases as described above support the fact that the drug was probably the cause of the increased residula urine and/or urinary retention. However, none of these four cases required any further medical or surgical intervention including catheterization. All resolved spontaneously. Therefore, these reported events are not alarming to this clinical reviewer. They will be included in the product labeling as adverse reactions, including a Precaution for use in patients with pre-existing bladder outlet obstruction.***

Constipation:
Constipation was reported as an AE in 7/271 (3%) of patients treated with placebo, 14/282 (5%) of patients treated with fesoterodine 4mg/day and 21/279 (8%) of those treated with fesoterodine 8mg/day. Most of these were mild to moderate in severity. Severe constipation was reported in 2 (1%) patients in each of the placebo and fesoterodine 8mg/day groups, and in 1 (<1%) subject in the fesoterodine 4mg/day group. None of the cases of constipation was an SAE. Both patients in the fesoterodine 8mg/day group discontinued as a result of constipation. Narratives for these 2 patients who withdrew as a result of constipation are presented below:

Patient # 14909, a 43-year-old, female, extensive metabolizer, reported moderate constipation 26 days after starting treatment with fesoterodine 8mg/day. Drug was withdrawn and the patient was recovering at the last contact with the trial site.

Patient # 14423 a 79-year-old, female, extensive metabolizer, reported severe constipation 17 days after starting treatment with fesoterodine 8mg/day. The subject recovered after drug was withdrawn.

> ***Reviewer's comment:*** ***In the opinion of this clinical reviewer, both these patients who developed constipation following chronic use of fesoterodine 8mg/day (a known adverse event associated with anti-cholinergic medications) did not result in an impaction or bowel obstruction. Neither patient required hospitalization nor additional medical intervention, The constipation was relieved on discontinuation of fesoterodine.***

Dry Eyes:
Dry eyes ("keratoconjunctivitis sicca") were reported in 2 (1%) patients treated with fesoterodine 4mg/day and 9 (3%) patients treated with fesoterodine 8mg/day. No placebo-treated patients reported dry eyes. All of these AEs were mild or moderate in intensity and none was an SAE.

One **patient # 13446** treated with fesoterodine 4mg/day discontinued as a result of moderate dry eyes as he voluntarily withdrew consent from participation in the trial.

No adverse event involving blurred vision or other vision-related problems were reported during this trial.

Tachycardia:
Tachycardia was reported as an adverse event for 2 fesoterodine-treated patients in this trial, although the heart rate never exceeded 100bpm in the first patient. Narratives for these patients follow:

Patient # 13017, a 47-year-old, female, extensive metabolizer, experienced mild sinus tachycardia after 73 days on fesoterodine 4mg/day. Her baseline heart rate was 82bpm. On Day 56, her ECG heart rate was 90bpm, and this had decreased to 79bpm at the following visit on Day 84, and 70bpm at the follow-up visit 15 days after the last dose of trial medication. The highest heart rate recorded for this subject during the trial was 89bpm, 28 days after starting treatment with fesoterodine. The dose was not changed, the subject completed the trial, and the event resolved.

Patient #13149 was a 40-year-old Caucasian female. Her medical history included sinusitis, endometriosis, melanoma left thigh and allergy to prochlorperazine. She entered the trial with the diagnosis of OAB. At the time of AE that led to withdrawal, the patient was not yet randomized to fesoterodine but had taken placebo for 12 days. At Visit 2, the patient developed tachycardia (102bpm) while still being in the Placebo Run-In Phase. The intensity of the AE was rated to be moderate. She was randomized to receive fesoterodine 8mg/day. After four days of being on fesoterodine, the patient withdrew consent from the trial due to tachycardia. The patient recovered from the tachycardia soon thereafter. The drug was discontinued. Tachycardia was not classified as a serious adverse event in this case. Due to the fact that the event also occurred prior to trial medication administration, the investigator and the sponsor assessed the AE not related to trial medication.

> ***Reviewer's comment: The clinical reviewer is in agreement with the investigator that the event of tachycardia in Patient #13149 existed prior to the administration of fesoterodine and also could have occurred as a result of other concomitant medications (i.e., pseudoephedrine) that were on board. Also, it is acknowleged that anti-muscarinic medications as a class are associated with some degree of tachycardia.***

No other medically relevant cardiac-related AEs were identified in this trial. No AEs of palpitation were reported in this trial.

Routine Clinical Laboratory Evaluations:
The majority of patients in all treatment groups had normal values at baseline and these remained normal until the end of the treatment period for all parameters. There were no apparent trends in shifts of laboratory parameters of clinical relevance.
The following table shows all clinical laboratory abnormalities in this trial reported as adverse events.

Appendix A. Table 11.

Summary of laboratory abnormalities reported as adverse events during treatment in at least 1 subject treated with fesoterodine (SS in SP584)

Laboratory category / preferred term	Placebo N=271 n (%)	Feso 4mg/day N=282 n (%)	Feso 8mg/day N=279 n (%)
Hematology			
Neutrophil count decreased	0	0	2 (1)
Anemia	0	0	1 (<1)
Hematocrit decreased	0	1 (<1)	1 (<1)
White blood cell count increased	1 (<1)	1 (<1)	0
Differential white blood cell count abnormal	0	1 (<1)	0
Hemoglobin decreased	0	1 (<1)	0
Blood chemistry			
Blood creatine phosphokinase increased	3 (1)	4 (1)	3 (1)
Blood triglycerides increased	1 (<1)	2 (1)	3 (1)
Gamma-glutamyltransferase increased	2 (1)	1 (<1)	3 (1)
Blood potassium increased	0	2 (1)	2 (1)
Aspartate aminotransferase increased	1 (<1)	0	2 (1)
Hypercholesterolemia	0	0	2 (1)
Alanine aminotransferase increased	4 (2)	1 (<1)	1 (<1)
Liver function test abnormal	0	1 (<1)	1 (<1)[a]
Hypomagnesemia	0	1 (<1)	1 (<1)
Hyperalbuminemia	0	0	1 (<1)
Hyperlipidemia	0	0	1 (<1)
Blood creatinine increased	0	0	1 (<1)
Blood lactate dehydrogenase increased	0	0	1 (<1)
Blood uric acid increased	1 (<1)	3 (1)	0
Blood cholesterol increased	2 (1)	2 (1)	0
Blood glucose increased	0	1 (<1)	0
Blood potassium decreased	0	1 (<1)	0
Hypocalcemia	0	1 (<1)	0
Hypokalemia	1 (<1)	1 (<1)	0
Protein total decreased	0	1 (<1)	0
Urinalysis/fecal findings			
White blood cells urine	0	1 (<1)	1 (<1)
Hematochezia	0	0	1 (<1)
Hematuria	1 (<1)	2 (1)	0
Glucose urine present	0	2 (1)	0
Blood urine	0	1 (<1)	0
Urea urine increased	0	1 (<1)	0
Fecal occult blood positive	0	1 (<1)	0

Feso=fesoterodine, SAE=serious adverse event, SS=safety set

As shown, no clinically relevant hematology, blood chemistry or urinalysis changes from baseline to Visit 6 (or the end of treatment) were reported for more than 2 patients in either fesoterodine group. No patient had ALT or AST ≥3×ULN or elevated bilirubin during treatment except for one patient, who withdrew from the trial as a result of elevated LFT's. This patient had other significant co-morbid medical conditions that appeared to have played a role in this event. The narrative is briefly described below:

Patient 14190, a 67-year-old, female, extensive metabolizer, had elevated alkaline phosphatase, AST, ALT, GGT, and bilirubin 23 days after the last dose of fesoterodine 8mg/day. This event was recorded as an AE (reported term "elevated liver function tests secondary to carcinoma of the intestines and pancreatic disease").

> ***Reviewer's comment:*** ***The increase in serum LFT's in patient # 14190 could be from the drug itself, but is more likely to be related to co-morbid medical condition of intestinal cancer and pancreatic disease. It is notable that the event was not reported until 23 days after the last dose of fesoterodine. This reviewer agrees with the investigator that fesoterodine may not be the cause of this event.***

There were a few isolated cases of increased transaminases reported as AEs. These were equally distributed among treatment groups; no trends were observed.

One patient had laboratory abnormalities reported as AEs that led to premature discontinuation from the trial. **Patient # 14569**, a 75-year-old female, extensive metabolizer, had severe "blood in stool" (coded to hematochezia) and moderate "abnormal kidney function", which are not reflected in the previous table. These occurred after 50 days of treatment with fesoterodine 8mg/day. Blood chemistry results showed that BUN was elevated at Visits 2 (baseline), 3, and 4; and uric acid was elevated at Visits 1, 2, 3, and 4. Trial medication was withdrawn and the patient discontinued the trial. The hematochezia resolved by 44 days after last dose and the renal impairment was ongoing. The investigator considered the kidney AE to be unlikely related to trial medication and the hematochezia to be unrelated.

Vital Signs:
No clinically relevant changes or trends were apparent in the mean changes from baseline for systolic or diastolic BP. There was a small, dose-dependent increase in heart rate from baseline to end of treatment in the fesoterodine-treatment groups: placebo=1bpm versus fesoterodine 4mg/day = 3bpm and fesoterodine 8mg/day = 4bpm. Metabolization status had no affect on changes in mean vital signs.

Appendix A. Table 12. Table of abnormal vital signs, by category and by treatment group.

Abnormal vital sign	Placebo N=269 n (%)	Feso 4mg/day N=279 n (%)	Feso 8mg/day N=277 n (%)
High systolic BP: BP ≥180 mmHg and increase of ≥20	2 (1)	2 (1)	2 (1)
Low systolic BP: ≤90 mmHg and decrease of ≥20 mmHg	1 (<1)	0	2 (1)
High diastolic BP: ≥105mmHg and increase of ≥15 mmHg	0	0	0
Low diastolic BP: ≤50mmHg and decrease of ≥15mmHg	4 (2)	0	2 (1)
High heart rate: ≥120bpm and increase of ≥15bpm	1 (<1)	0	2 (1)
Low heart rate: ≤50bpm and decrease of ≥15bpm	0	0	1 (<1)

BP=blood pressure, Feso=fesoterodine, SS=safety set

There was one patient treated with fesoterodine who experienced an adverse event of "elevated blood pressure" from the baseline. **Patient # 14914**, a 55-year-old, female, extensive metabolizer, experienced "elevated blood pressure" after 10 days on fesoterodine 4mg/day. Her BP at baseline was 154/90 and the highest BP recorded at a trial visit was 143/98 after 14 days on trial medication. The dose was not changed and the AE resolved while the subject remained in the trial.

> ***Reviewer's Comment:*** ***This patient had hypertension and baseline and this did not appear to increase while taking fesoterodine.***

EKGs:

The table below presents mean changes from baseline to endpoint in EKG intervals for each treatment group.

Appendix A. Table 13.

Change from Baseline at end of treatment (Visit 6 or last treatment) in 12-lead electrocardiogram results (SS in SP584)

Parameter	Placebo N=267 Mean (SD)	Feso 4mg/day N=279 Mean (SD)	Feso 8mg/day N=275 Mean (SD)
Heart rate (bpm)	0.3 (7.81)	3.8 (9.49)	5.3 (9.16)
PR interval[a] (ms)	-0.3 (17.99)	-2.2 (14.39)	-3.4 (17.51)
QRS duration (ms)	-0.4 (5.05)	-0.5 (6.60)	0.3 (8.61)
QT interval (ms)	-1.6 (20.31)	-6.5 (20.73)	-9.1 (21.02)
QTcF (ms)	-1.1 (15.89)	0.1 (15.68)	0.5 (14.86)
QTcB (ms)	-0.8 (18.68)	3.8 (19.40)	5.8 (17.53)

Feso=fesoterodine, QTcB=QTc Bazett, QTcF= QTc Fridericia, SS=safety set

During the process of this trial, a marginal increase (2-7bpm) in mean heart rate was observed in patients receiving fesoterodine. The increase was larger in the 8mg/day group.

> ***Reviewer's Comment**: Increased heart rate is a known effect of antimuscarinic drugs.*

Additionally, QTc values were calculated according to the Fridericia and Bazett formulas. When analyzed according to the Fridericia method, the placebo and fesoterodine groups had minimal changes from baseline throughout the trial, i.e., the mean changes from baseline at end of treatment was -1.1ms for placebo, 0.1ms for fesoterodine 4mg/day, and 0.5ms for fesoterodine 8mg/day. The highest mean change from baseline for any post-baseline measurement was 10ms in all treatment groups. When analyzed according to the Bazett formula, small (2-7ms) dose-related increases from baseline were seen in both fesoterodine treatment groups compared to the placebo group. Analysis of QTc changes of ≥60ms from baseline did not indicate any fesoterodine induced prolongation on QTc interval using either Bazett's or Fridericia's formulas. Instances of QTc changes of ≥60ms from baseline occurred more frequently in the placebo group than in either of the fesoterodine treatment groups.

Overall, in this trial there was no evidence that administration of fesoterodine results in QTc prolongation. In many cases, the increases seen using the Bazett correction were no longer evident when using the Fridericia formula, which may be due to the fact that the Bazett formula tends to overcorrect at higher heart rates.

> ***Reviewer's Comment**: It is a well known that QTcB overcorrects the QT interval in cases with increased heart rate and therefore this result is secondary to the increase in heart rate following treatment with fesoterodine. Further, the*

thorough QT study (See Appendix C) did not show an effect of fesoterodine on the corrected QT interval.

For other 12-lead ECG interval parameters i.e., PR interval, QRS duration, and QT interval, there were minimal mean changes from baseline at each visit. Increase in the heart rate was found in one patient on fesoterodine 8mg/day from baseline of 85bpm to 117bpm. This increase was noted on ECG and was asymptomatic. Narrative for this patient is presented below.

Patient # 14312, a 62-year-old, female, extensive metabolizer, had an AE that coded to the preferred term "heart rate increased" after receiving fesoterodine 8mg/day for 21 days. The patient's heart rate was 85bpm at baseline and on the day of the AE, her heart rate was 117bpm. This patients heart rate remained mildly elevated throughout the trial and resolved by 32 days after the patient discontinued trial medication as a result of worsening dry mouth that started after the patient had been taking fesoterodine 8mg/day for 70 days.

Physical Examinations:
At screening, most patients had normal findings for each of the individual parameters of physical examination. In most cases, physical examination results at end of trial were the same as noted at baseline, or shifted from abnormal to normal. Shifts from normal to abnormal were noted with a similar incidence across the 3 treatment groups. The shifts most frequently reported involved the "eyes, ears, nose, mouth, throat" system organ class and shifts from normal to abnormal were reported in 1%, 1%, and 2% of patients in the placebo, fesoterodine 4mg/day, and fesoterodine 8mg/day groups.

Reviewer's Safety Summary for SP584:
Treatment-emergent AE's were reported for 149/271 (55%) of patients in the placebo group, 171/282 (61%) of patients in the fesoterodine 4mg/day group, and 193/279 (69%) of patients in the fesoterodine 8mg/day group. Adverse events that were more common in patients treated with either dose of fesoterodine than in placebo included (in descending order of frequency for fesoterodine 8mg/day) **dry mouth, constipation, urinary tract infection, keratoconjunctivitis sicca (dry eyes), headache, urinary retention, nasopharyngitis** and **hypertension**. Of these, dry mouth, constipation, urinary tract infection, dry eyes, nausea, and urinary retention were more common at 8mg/day than at 4mg/day. Most AE's were mild in intensity. The most common AE's considered to be related to trial medication by the investigators are common with the use of marketed antimuscarinic compounds (eg, dry mouth, constipation, dry eyes, urinary retention).

There were no deaths in this trial.

A total of 2 - 3% of patients in each treatment group had SAE's during the trial. One placebo-treated patient and 3 fesoterodine-treated patients from the trial were considered by the investigator to be at least possibly related to trial medication.

A total of 53 patients discontinued due to AE's during treatment i.e., 11/271 patients (4%) in the placebo group, 17/282 patients (6%) in the fesoterodine 4mg/day group, and 25/279 patients (9%) in the fesoterodine 8mg/day group. Adverse events that resulted in discontinuation in >1% of patients in any treatment group included dry mouth (1.1% in fesoterodine 4mg/day, 1.8% in fesoterodine 8mg/day) and urinary retention (1.1% in fesoterodine 8mg/day).

The AE profiles during the treatment period for patients ≥65 years of age and for CYP2D6 poor metabolizers were generally similar to that of the overall population during that period. Dry mouth was reported for 40% of patients ≥65 years of age taking fesoterodine 8mg/day compared to 33% of patients <65 years of age at those doses. Constipation was reported for 16% of patients ≥65 years of age taking fesoterodine 8mg/day compared to 3% of patients <65 years of age at this dose. Dry mouth and dry eyes were reported more frequently among poor metabolizers than among the population as a whole, although interpretation of these results is limited due to the small number of patients in this subgroup.

Overall, clinical laboratory results were consistent across the 3 treatment groups. No treatment appeared to affect any laboratory parameter in a medically relevant manner when comparing treatment groups. No patient had ALT or AST ≥3×ULN (upper limit of normal range) with elevated bilirubin during treatment. No laboratory value-associated AE was reported for >1% of patients in any treatment group.

With regard to vital signs, marginal dose-dependent increases (2-7bpm) in mean heart rate were noted both in the vital signs and measured via ECG, as might be expected with anti-muscarinic drug treatment. Similar rates of hypertension were reported for patients treated with placebo (2%) and those treated with fesoterodine 4mg/day (3%) and no AE's of hypertension were reported for patients receiving fesoterodine 8mg/day. There was no drug-related effects on blood pressure.

When QTc was analyzed according to the Fridericia method, the placebo and fesoterodine groups had minimal QTc changes (≤1ms in each treatment group) from baseline throughout the trial. Absolute values of ≥500ms or changes from baseline of ≥60ms in QTc (B or F) intervals were more common in the placebo group than in the fesoterodine groups. One patient in the fesoterodine 4mg/day group had QTcF ≥500ms and change from baseline of ≥60ms and 1 patient in the fesoterodine 8mg/day group had a QTcF change from Baseline of ≥60ms.

For the PR interval, QRS duration and QT interval, there were small mean changes from baseline at each visit and there were no differences in the mean values between treatment groups or temporally related trends in these mean values. Mild sinus tachycardia (90bpm) was reported as an AE for 1 fesoterodine-treated subject (4mg/day group).

While there were minor changes in vital signs and ECG results (increase in heart rate), there was no evidence of increased cardiovascular risk due to treatment with fesoterodine in this trial.

Mean increases in residual urine volumes were small (post-baseline mean ranges≤36mL) in each treatment group and were expected. A total of 8 patients (about 1% of 146 fesoterodine-treated patients) had residual urine volumes >200mL during the trial (highest post dose value=392mL); all but 1 of these were in the fesoterodine 8mg/day group.

Fesoterodine 4 and 8mg/day were well tolerated in this population of trial patients. A total of 83 - 89% of patients in each treatment group had their tolerance assessed as "excellent" or "good" at their last on-treatment visit.

Reviewer's Safety Conclusions for SP584:

- In this trial, sustained-release fesoterodine (4 and 8mg/day) were generally well tolerated when administered for 12 weeks.

- The most frequently reported AE's were those that are typical for anti-muscarinic drugs. Adverse events included dry mouth, constipation, urinary tract infection, dry eyes, and urinary retention. They were generally mild to moderate in intensity. The incidence of discontinuations due to AE's in the placebo and fesoterodine 4mg/day treatment groups was comparable (placebo: 4%; fesoterodine 4mg/day: 6%), while the rate of discontinuation was slightly higher in the fesoterodine 8mg/day group (9%).

- Overall, the clinical laboratory results were consistent across the 3 treatment groups. No treatment appeared to adversely affect any laboratory value measured during the course of the trial. Regarding serum transaminases, there was an individual case that exceeded the normal range, but no patient had ALT or AST ≥3×ULN with elevated bilirubin during treatment.

- Marginal dose-dependent increases (2-7bpm) in mean heart rate were noted both in the vital signs measurement and in the ECG. There was no effect on blood pressure, as measured during vital signs. There was no evidence of additional cardiovascular risk due to fesoterodine in this trial.

- While dry mouth and constipation were more frequent in the geriatric population, age ≥65 years and CYP2D6 metabolization status did not affect the fesoterodine safety profile in a medically relevant manner.

Efficacy Results:

Primary and co-primary efficacy endpoints:
The co-primary efficacy variables as agreed by the Division were the change in the number of micturitions (frequency) per 24 hours after 12 weeks of treatment and the

change in the number of urge incontinence episodes per 24 hours after 12 weeks of treatment in patients with incontinence at baseline.

For change in the number of urge incontinence episodes, only those patients who were incontinent at baseline were included in the analysis.

The table below presents the sponsor's descriptive summary for the change in average number from baseline in micturitions per 24 hours and urge incontinence episodes per 24 hours. Patients in each treatment group had baseline means of 12 - 13 micturitions per 24 hours and 4 urge incontinence episodes per 24 hours.

Appendix A. Table 14. Changes from baseline for number of micturitions and urge incontinence episodes per 24 hours at end of treatment.

Variable	Placebo	Feso 4mg/day	Feso 8mg/day
Number of micturitions per 24 hours mean change (SD)	N=266 -1.02 (3.387)	N=267 -1.86 (3.645)	N=267 -1.94 (2.974)
Number of urge incontinence episodes per 24 hours[b] mean change (SD)	N=205 -1.00 (2.749)	N=228 -1.77 (3.163)	N=218 -2.42 (2.764)
Treatment response (responder rate)	N=266 120 (45%)	N=267 170 (64%)	N=267 198 (74%)

FAS=full analysis set, Feso=fesoterodine, LOCF=last observation carried forward, SD=standard deviation

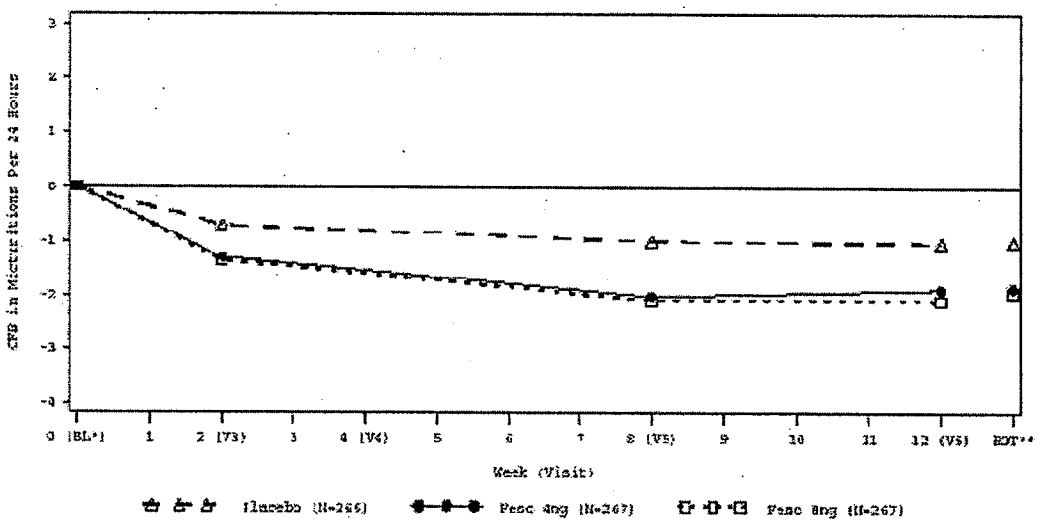
Fesoterodine decreased the number of micturitions and urge incontinence episodes per 24 hours during this trial. The decreases in the number of micturitions and number of urge incontinence episodes per 24 hours in the fesoterodine 4mg/day and 8mg/day groups were significant compared to those in the placebo group.

Statistically significant improvements in [redacted] co-primary variables were observed at the first post-dose measurement, ie, as early as 2 weeks after commencement of treatment, for the 8mg dose. For the 4mg dose, statistically significant improvements were seen at Week 2 [redacted] for the incontinence endpoint. b(4)

Frequency of Micturitions:
The following figure and table shows the change-from baseline in number of micturitions per 24 hours.

Appears This Way
On Original

Appendix A. Figure 1. Change from baseline in average frequency of micturitions per 24 hours for each visit.



Appendix A. Table 15. Change from baseline to endpoint in average frequency of micturitions per 24 hours.

SP584/Primary Endpoint: Micturitions per 24 hours*

	Placebo (n=266)	Feso 4 mg (n=267)	Feso 8 mg (n=267)
Baseline	12.2 (3.7)	12.9 (3.9)	12.0 (3.3)
Endpoint	11.2 (3.4)	11.0 (3.6)	10.1(3.2)
Change from baseline	- 1.02 (3.4)	-1.86 (3.6)	-1.94 (3.0)
P value for change from baseline vs. placebo		p=0.032	P <0.001

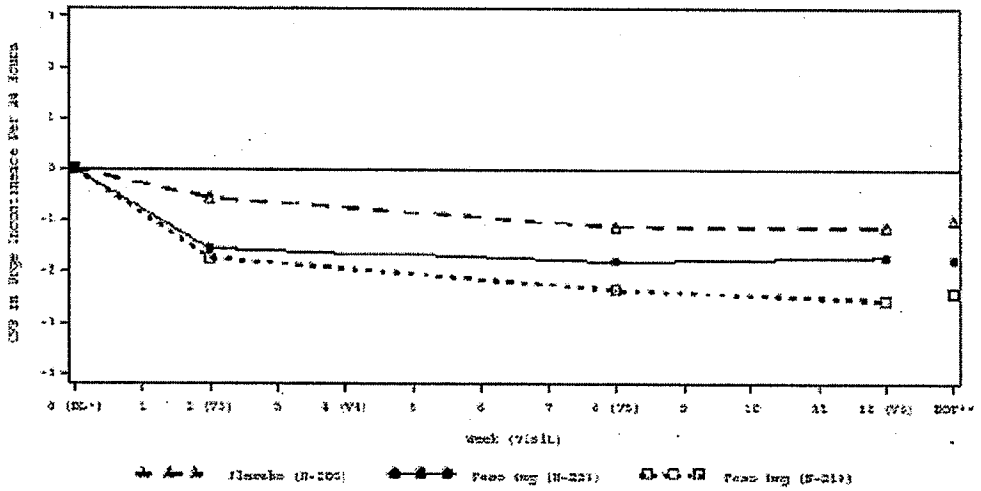
*Mean (SD) – Sample size reflects number of subjects at BL.
Analysis reflects BL to Endpoint using LOCF

The mean changes from baseline in the average number of micturitions per 24 hours as seen in Appendix A. Table 15. above were -1.86 and -1.94 (denoting an improvement) in the fesoterodine 4 and 8mg/day treatment groups, respectively, compared to -1.0 in the placebo group. These reflect statistically significant difference between groups for change from baseline to the endpoint using last observation carried forward (LOCF).

Urge Incontinence Episode Frequency:
The following figure and table shows the change-from baseline in number of urge incontinence episodes per 24 hours (in patients with incontinence at baseline).

Appendix A. Figure 2.

Change from Baseline in average number of urge incontinence episodes per 24 hours for each visit by randomized treatment population (FAS in SP584)



CFB=change from Baseline, FAS=full analysis set, Feso=Fesoterodine, LOCF=last observation carried forward

Appendix A. Table 16. Change from baseline to endpoint in average number of urge incontinence episodes per 24 hours (in patients with incontinence at baseline).

SP584/Secondary Endpoint: Incontinence Episodes per 24 hours*

	Placebo (n=205)	Feso 4 mg (n=228)	Feso 8 mg (n=218)
Baseline	3.7 (3.3)	3.9 (3.5)	3.9 (3.3)
Endpoint	2.7 (3.3)	2.1 (3.2)	1.4 (2.1)
Change from baseline	-1.0 (2.7)	-1.77 (3.1)	-2.42 (2.8)
P value for change from baseline vs. placebo		p=0.002	P <0.001

Mean (SD) – Sample size reflects number of subjects at BL
Analysis reflects BL to Endpoint using LOCF

The mean changes from baseline in the average number of urge incontinence episodes per 24 hours as seen in the graph and the Table above were -1.8 and -2.4 (denoting improvement) in the fesoterodine 4 and 8mg/day treatment groups respectively compared to -1.0 in the placebo group. This reflects a statistically significant difference between groups using last observation carried forward (LOCF).

Average Voided Volume:
The following table shows the change-from baseline in average voided volume per micturition, as measured for one of the three diary days.

Appendix A. Table 17. Change from baseline to endpoint in average volume voided per micturition.

SP584/Secondary Endpoint: Voided Volume*

	Placebo (n=266)	Feso 4 mg (n=267)	Feso 8 mg (n=267)
Baseline	159.4 (69.0)	152.0 (60.2)	155.9 (57.7)
Endpoint	167.5 (95.7)	169.5 (78.0)	189.3 (77.4)
Change from baseline	7.9 (69.4)	17.0 (61.1)	33.4 (62.5)
P value for change from baseline vs. placebo		p=0.15	P < 0.001

Mean (SD) – Sample size reflects number of subjects at BL
Analysis reflects BL to Endpoint using LOCF

The mean change from baseline in volume voided as seen in the Table above were 17ml and 33.4ml (increase in volume denoting improvement) in the fesoterodine 4 and 8mg/day treatment groups respectively compared to 8ml in the placebo group. This reflects a statistically significant difference between groups for the 8mg/day group compared to placebo using last observation carried forward (LOCF). Use of fesoterodine increased (improved) mean voided volume per micturition in a dose dependent manner during this trial.

> ***Reviewer's Comment:*** ***The endpoints above show a decrease in the frequency of micturition per 24 hours, a decrease in the incontinence episodes per 24 hours and a dose-dependent increase in the volume voided. The change from baseline to the endpoint, i.e., 12 weeks as seen in the key efficacy variables represents an overall improvement in OAB symptoms with use of fesoterodine.***

Additional Exploratory Efficacy Analyses:

Micturitions:
As shown in the previous summary tables, the frequency of micturitions per 24 hours for patients in the full analysis set (FAS) with LOCF who dropped out/imputed cases was decreased **(improved)** compared to baseline and this difference from baseline was more pronounced in patients receiving fesoterodine 4 and 8mg/day compared to placebo. There were no dose-dependent treatment differences compared to placebo.

When outliers were *excluded* from the FAS with LOCF, the frequency of micturitions per 24 hours was consistent with the results of the primary analysis ($p \leq 0.009$).

Use of fesoterodine decreased **(improved)** the mean number of micturitions during daytime in a dose-dependent manner during this trial. At baseline each treatment group had a mean of 10 to 11 micturitions during daytime. The reduction from baseline to end of treatment for the FAS in the mean number of micturitions during daytime was about twice as large for the fesoterodine groups (feso 4mg/day= -1.24; feso 8mg/day= -1.46) compared to the placebo group (- 0.66).

Use of fesoterodine decreased **(improved)** the mean number of micturitions during sleeping time during this trial. At baseline, each treatment group had a low number (mean of 2) of micturitions during sleeping time. The mean decreases from baseline to end of treatment in the mean number of micturitions during sleeping time for the FAS were -0.36 in the placebo group, and -0.62 and -0.48 in the fesoterodine 4 and 8mg/day groups respectively.

Incontinence Episode Frequency:
As shown in the previous tables and figures, fesoterodine reduced **(improved)** the number of episodes with urge incontinence per 24 hours (in patients with incontinence at baseline) in a dose-dependent manner during this trial.

At baseline, patients in all treatment groups had a mean of 4 episodes of incontinence per 24 hours. The mean reductions from baseline to end of treatment for the FAS in the number of episodes of incontinence among incontinent patients for the FAS were -1.00 in the placebo group, and -1.77 and -2.42 in the fesoterodine 4 and 8mg/day groups, respectively.

Fesoterodine increased **(improved)** the mean number of continent days per week in a dose dependent manner in this trial. While the mean number of continent days per week was less than 1 (0.6 – 0.7 days) in all 3 treatment groups at baseline, the mean number of continent day per week at the end of treatment was 1.4 days in the placebo group and 2.4 and 2.8 days in the fesoterodine 4 and 8mg/day groups, respectively.

Reviewer's Efficacy Conclusions:
Fesoterodine 4 and 8mg administered once daily for 12 weeks improved all three variables (change in the number of micturitions per 24 hours, change in the number of urge incontinence episodes per 24 hours, and volume voided) in a statistically significant manner compared to placebo treatment. In addition to improvements in the key variables, fesoterodine also improved the signs and symptoms of OAB for other secondary endpoints and other exploratory analyses. In the opinion of the reviewer, the results shown rise to the level of symptomatic relief for OAB.

Dose-dependent responses to fesoterodine 4 and 8mg/day were observed for all three efficacy variables. Statistically significant improvements in incontinence was observed as early as 2 weeks after commencement of treatment (at the first efficacy evaluation) for both doses. b(4)

b(4)

Prior drug treatment for OAB, age, or gender did not affect fesoterodine efficacy in a medically relevant manner.

In the opinion of the reviewer, the efficacy results for fesoterodine in this trial rise to the level of symptomatic relief for OAB.

APPENDIX – B

Medical Officer's Review of Fesoterodine
Phase 3 Study (SP583)

NDA 22-030

Date of Submission:	**March 27, 2006**
NDA Goal Date:	**January 27, 2007**
Action Date:	**January 26, 2007**
Sponsor:	**Schwarz Biosciences, Inc.**
Drug Name:	
Proposed Name:	**Fesoterodine**
Proposed Trade Name:	[redacted] b(4)
Pharmacologic Category:	**Anti-Cholinergic (Muscarinic Receptor Antagonist)**
Study Number:	**SP583**
Development Phase:	**3**
Trial Initiation Date:	**January 31, 2004**
Trial Completion Date:	**February 25, 2005**
Indication:	**Treatment of Overactive Bladder (OAB)**
Doses Used:	**4mg & 8mg once a day**
Route of Administration:	**Oral**
Active Control Used:	**Tolterodine 4mg**

Study in Brief:
This was a phase 3, parallel group, randomized, double blind, placebo and active-controlled, multi-center European trial designed to investigate the efficacy, tolerability and safety of fesoterodine in patients with OAB. According to the Sponsor, inclusion of the active control, tolterodine 4mg/day, was at the request of European regulatory authorities. This study was conducted concurrently with the U.S. pivotal Phase 3 study SP583.

Background:
Therapy for OAB focuses on symptomatic treatment since the underlying cause for the condition is not known in most non-neurogenic cases. The basic treatments for OAB are either non-drug treatment such as behavioral training, use of incontinence pads or other protective equipment, sacral nerve stimulation, or the use of anti-muscarinic drugs These drugs antagonize the acetylcholine-induced stimulation of postganglionic muscarinic receptors. Muscarinic receptors are thought to mediate not only the detrusor

contractions of normal voiding but also the main part of contraction in OAB associated with urge and urge incontinence.

Overactive bladder affects at least 10% of the overall adult population. The prevalence of detrusor overactivity increases with age, and 40% of all individuals over the age of 50 have some form of detrusor overactivity, rising to 60% - 80% in institutionalized patients. The majority of patients are women.

Clinical Review Methods:
This Phase 3 clinical study report (**SP583**) was reviewed in detail, with special emphasis on the efficacy results and safety evaluations. Efficacy and safety data were derived from the Clinical Trial Report (**SP583**) dated 13 Oct 2005. Pharmacokinetics were not assessed in this trial.

Overview of Study Protocol:

Objectives:
The objective of the trial was to investigate the efficacy, tolerability and safety of fesoterodine compared with placebo and active control in patients with OAB.

The specific efficacy objectives were to assess the co-primary efficacy variables which were: change in average number of micturitions/24 hours from baseline to the end of study (i.e. 12 weeks) and change in average number of urge incontinence episodes/24 hours from baseline to the end of study treatment (i.e. 12 weeks). Additional efficacy objectives included measurement of "treatment response", which was derived from a treatment benefit scale measuring subjective improvement (yes/no) during the double-blind treatment period.

Study Design:
This was a randomized, double-blind, placebo-and active-controlled, Phase 3 trial of fesoterodine SR in adult male and female patients with OAB. The trial was initiated on [redacted] and was completed [redacted] The trial was conducted in a total of 1135 patients with OAB at multiple sites in 16 European countries. Patients first entered a 2-week Run-In period, wherein placebo capsule and tablet were administered each morning. Patients still eligible at the end of the Run-In period entered a 12-week Double-Blind, Double-Dummy Treatment period, wherein patients received either fesoterodine 4 mg or 8 mg/day, placebo, or tolterodine 4 mg/day. Efficacy and safety assessments were conducted at routine follow-up visits at Weeks 2, 4, 8 and 12. b(4)

For purposes of U.S. regulatory approval, the co-primary efficacy endpoint assessments were: change in average number of micturitions/24 hours from baseline to the end of study (i.e. 12 weeks) and change in average number of urge incontinence episodes/24 hours from baseline to the end of study treatment (i.e. 12 weeks).

The secondary efficacy endpoint assessments included:

1. Change from baseline in average voided volume per micturition.
2. Change from baseline in average number of voids during the day and at night.
3. Change from baseline in nocturia episodes in those voiding more than 33 % of their total volume at night.
4. Change from baseline in average number of total "urgency episodes" per 24 hrs.
5. Change from baseline in number of "continent days".
6. Change from baseline in the severity of urinary urgency.
7. "Treatment Response", defined as "yes, improved" versus "no, not improved".

Safety assessments included periodic collection and measurement of: clinical AE's, routine laboratory and urinalysis parameters, vital signs, ECGs, physical examinations, residual urine volume, and treatment "tolerance".

Inclusion Criteria:

At Enrollment

1. Informed consent.
2. Ability to comply with trial requirements.
3. Minimum 6-month history of OAB or urge incontinence.
4. Minimum of 8 micturitions per day.
5. Minimum of 18 years of age.
6. Women of child-bearing potential must have had a negative pregnancy test and must use contraception.

At Randomization

1. Completion of voiding diary for 3 consecutive days during the week prior to visit 2.
2. Minimum of 3 urge incontinence episodes documented in the Run-In period.
3. Minimum of 8 micturitions per 24 hours during the Run-In period.
4. Documention of voiding volume assessments for 24 hours during the 3-day diary period.
5. Based on Likert scale, the condition causes at least "moderate problems".
6. Women of child-bearing potential must have had a negative pregnancy test. and must use contraception.

Exclusion Criteria:

At Enrollment

1. Prior randomization in a trial using this drug.
2. Participation in another drug trial currently or within the past 30 days.
3. History of alcohol or drug abuse currently or within the past 6 months.
4. Known medical condition that could compromise ability to participate in the trial.
5. Hypersensitivity to trial medications or contraindications to use of tolterodine.
6. Pregnant or breast-feeding.
7. Known neurological disease influencing bladder function.

8. Known urinary tract pathology that could potentially be responsible for urge or incontinence.
9. Pelvic prolapse: Baden's grade III or above.
10. Active or persistent urinary tract infection at Visit 1, or history of recurrent UTI's.
11. Polyuria, defined as >3000mL per day.
12. Residual urine volume > 100 ml.
13. Increased urinary frequency and/or nocturia due to renal insufficiency or heart failure.
14. Clinically relevant bladder outlet obstruction.
15. Severe cerebral artery stenosis, or severe renal and/or hepatic diseases.
16. Obstructive GI disease, inflammatory bowel disease, megacolon, atony, or ileus.
17. Myasthenia gravis, angle-closure glaucoma, or narrow anterior chamber angles.
18. Clinically relevant arrhythmia and/or unstable angina and/or other unstable CV conditions, or existence of indwelling pacemaker.
19. QTcB interval of > 500 ms.
20. Current or within 2 weeks prior to visit 1, treatment with medications for OAB, class Ia and class III antiarrhythmic drugs, or amantadine.
21. Current or within 4 weeks prior to Visit 1, electrostimulation, bladder training or physiotherapy aimed to improve bladder function.
22. Started treatment with tricyclic and tetracyclic antidepressants, neuroleptics, or estrogen replacement therapy within 4 weeks prior to Visit 1 and/or is not on a stable dose.

At Enrollment

1. Incomplete 3-day voiding diary or missing voided volume.
2. Residual urine volume> 100 mL, or polyuria (total daily urine output >3L), or voided volume > 500 ml for any single micturition during the Run-In period.
3. Active UTI at Visit 2, or predominantly symptoms of stress incontinence.
4. Clinically relevant arrhythmia and/or unstable angina and/or other unstable CV conditions.
5. QTcB interval of > 500 ms as shown by Visit 1 ECG analysis, or any 1 of the 2 QTc values at Visit 2.
6. Serum creatinine $\geq$ 1.6 mg/dL, serum bilirubin $\geq$ 1.5 mg/dL, or serum ALT,AST or GGT $\geq$ 2 x upper limit of normal range.
7. Clinically relevant abnormal values for hematology or serum chemistry at Visit 1, or abnormal urinalysis at Visit 2.

Efficacy Results

As shown in the following reviewer's summary efficacy tables, treatment with both doses of fesoterodine demonstrated statistically significant improvements from baseline to end of treatment as compared to placebo for both the micturition and urge incontinence co-primary efficacy variables. The analysis of these results was conducted using least squares means (LS Means), last observation carried forward (LOCF) imputation methodology, and analysis of the covariance (ANCOVA).

Appendix B. Table 1: Summary Results for Change from Baseline in Average Number of Micturitons per 24 hours (SP583).

Treatment (N)	BL →Endpt (LS Means)	Compared To:	Treatment Difference	95% CI
Placebo (279)	-0.95	*N/A*	*N/A*	*N/A*
Feso 4mg (265)	-1.76	Placebo	-0.81	(-1.26, -0.36)
Feso 8mg (276)	-1.88	Placebo	-0.93	(-1.38, -0.49)
Tolterodine (283)	-1.73	Placebo	-0.78	(-1.23, -0.34)

BL=Baseline, Endpt=Endpoint, LS Means= Least Squares, CI = Confidence Interval

Appendix B. Table 2: Summary Results for Change from Baseline in Average Number of Urge Incontinence Episodes per 24 hours (in those patients with incontinence at baseline) (SP583).

Treatment (N)	BL →Endpt (LS Means)	Compared To:	Treatment Difference	95% CI
Placebo (211)	-1.14	*N/A*	*N/A*	*N/A*
Feso 4mg (199)	-1.95	Placebo	-0.81	(-1.26, -0.35)
Feso 8mg (223)	-2.22	Placebo	-1.08	(-1.52, -0.64)
Tolterodine (223)	-1.74	Placebo	-0.60	(-1.04, -0.16)

BL=Baseline, Endpt=Endpoint, LS Means= Least Squares, CI = Confidence Interval

The following tables summarize the percentage of Treatment Responders. In this trial, treatment response was defined by a "Global" patient-reported outcome. The patient gave a categorical impression of whether they were improved or not at Week 12. Those that stated improvement were defined as "Responders".

Appendix B. Table 3: Summary of results for "Treatment Response" (Improved or Not Improved) at Week 12 in Study SP583. Missing values imputed by LOCF.

Treatment (N)	Responders (%)	Compared To:	Treatment Difference	95% CI
Placebo (279)	149 (53.4%)	*N/A*	*N/A*	*N/A*
Feso 4mg (265)	198 (74.7%)	Placebo	21.3%	(13.5, 29.2)
Feso 8mg (276)	218 (79.0%)	Placebo	25.6%	(18.0, 33.2)
Tolterodine (283)	205 (72.4%)	Placebo	19.4	(11.2, 26.9)

LOCF=Last Observation Carried Forward, CI = Confidence Interval

Appendix B. Table 4: Summary of results for "Treatment Response" (Improved or Not Improved) at Week 12 in Study SP583. Missing values imputed as non-response.

Treatment (N)	Responders (%)	Compared To:	Treatment Difference	95% CI
Placebo (279)	145 (52.0%)	*N/A*	*N/A*	*N/A*

Feso 4mg (265)	194 (73.2%)	Placebo	21.2%	(13.3, 29.2)
Feso 8mg (276)	214 (77.5%)	Placebo	25.6%	(17.9, 33.2)
Tolterodine (283)	205 (72.4%)	Placebo	19.4	(11.2, 26.9)

CI = Confidence Interval

> ***Reviewer's Comments:*** ***The sponsor has indeed demonstrated statistically significant improvement of both co-primary endpoints (micturitions and urge incontinence episodes) for fesoterodine over placebo. This trial reemphasizes that significant placebo effects are observed in controlled clinical trials for the treatment of OAB. It is also notable that the results for fesoterodine and the active control tolterodine were similar, although this study was not specifically designed to make formal statistical comparisons.***

Similar to the U.S. Phase 3 study report, this report also included results from other secondary efficacy endpoints, including change-from-baseline in average voided volume, and other exploratory patient-reported outcome instruments (PROs). The sponsor referred to the results of these PROs as "health outcome parameters" (or results from "Quality of Life" instruments). "Quality of Life" was assessed using two questionnaires, one focused on patients' "satisfaction" with treatment, and the other on patients' assessment of how problematic their OAB condition was to them. The latter instrument employed a 6-point Likert scale. In this study, fesoterodine improved the signs and symptoms of OAB for all "health outcome parameters" in a dose dependent manner.

Reviewer's Efficacy Conclusions:

The results of this trial **(SP583)** successfully demonstrated that fesoterodine at doses of 4 and 8 mg/daily was effective in reducing both the average number of micturitions and urge incontinence episodes/24hour periods during 12 week study compared with placebo. The efficacy appeared comparable to that of the approved agent, tolterodine, in this study.

b(4)

~~It~~ is the opinion of this reviewer that the results of this study support the clinical efficacy of fesoterodine.

Safety Results

Brief Summary of Findings

Fesoterodine SR (4 and 8 mg/day) was generally well tolerated for the treatment duration of 12 weeks. The most frequently reported clinical AE's were those seen with other anti-muscarinics in its class. No clinical AE resulted in withdrawal of > 1 % of patients in any treatment group. Changes in laboratory values were consistent across the 4 treatment groups, and there were no clinically relevant changes in any specific parameter. Overall, for all of the safety variables that were monitored, there were no clinically relevant differences between treatment groups. Herein, safety results for this study are summarized in more detail:

Overall Treatment-Emergent Adverse Events (TEAEs)
The overall treatment-emergent adverse event reports revealed a safety profile consistent with the anti-muscurinic class. The most commonly reported AEs in this study were: dry mouth, constipation, headache, dizziness, dry eyes, and fatigue. The following table summarizes the all-causality AE reports:

Appendix B. Table 5. Summary of all-causality treatment-emergent AE's reported by ≥2% of patients in a treatment group (SP583).

Adverse Event Terms	Placebo (n=283) %	Fesoterodine 4mg/day (n=272) %	Fesoterodine 8mg/day (n=287) %	Tolterodine 4mg/day (n=290) %
Dry Mouth	7%	22%	34%	17%
Constipation	1%	3%	5%	3%
Headache	5%	4%	2%	5%
Dizziness	3%	2%	1%	4%
Dry Eyes	0	2%	4%	1%
Fatigue	<1%	<1%	<1%	3%
UTI	2%	3%	3%	1%
Dyspepsia	1%	2%	3%	2%
Dry Throat	0	<1%	3%	1%
Nausea	<1%	<1%	1%	2%
Influenza	2%	3%	1%	1%
ALT Abnormal	<1%	1%	2%	0

Deaths:
There was 1 death reported in this study, judged by the investigator to be unrelated to study medication. The patients had completed treatment at a fesoterodine dose of 8mg per day, and was hospitalized only during the safety follow-up period as a consequence of bronchitis. The patients was discharged from the hospital after 8 days and died the following day from a myocardial infarction, 26 days after discontinuation of study medication.

> ***Reviewer's Comments:*** ***In the reviewer's opinion, this death did not appear to be related to fesoterodine.***

Serious Adverse Events (SAEs):
A total of 8 patients (2- 4 % of each treatment group) reported had SAE's during the trial that were considered to be at least possibly related to study drug and resulted in patient withdrawal. These events are summarized in the following table.

Appendix B. Table 6. All serious adverse events judged by the investigator to be at least possibly related to study medication and resulted in patient's withdrawal (SP583).

Treatment	Age/ Gender	SAE Term	Days on Drug	Intensity	Duration (Days)
Placebo	76M	ECG Abnormal	54	severe	21
	54F	Acute hepatitis	46	moderate	26
	54F	Headache	46	severe	4
Feso 4mg	48F	Chest Pain	16	mild	4
	52F	Gastroenteritis	5	severe	2
Feso 8mg	72M	Prolonged QT	57	mild	32
	70M	Angina Pectoris	1day after study	severe	5
Tolterodine	55F	Suprapubic Pain	45	severe	18

Discontinuations due to Adverse Events (AEs):
A total of 36 patients were withdrawn from this study due to AE's: 2 % in the placebo group, 3 % in the fesoterodine 4 mg group, 5% in the fesoterodine 8 mg group, and 3 % in the tolterodine group respectively.

Adverse events that resulted in discontinuation of > 1 patients in any treatment group included: prolonged QT (1 patient in the fesoterodine 4 mg/day group and 2 in fesoterodine 8 mg/day group, urinary retention (1 patient in the fesoterodine 4 mg/day group, and 2 in the fesoterodine 8 mg/day group), and mucosal dryness (2 patients in the fesoterodine 8 mg/day group). A summary of those specific AE's leading to discontinuation in >1 patient in any treatment group is shown in the table below.

Appendix B. Table 7. Summary of patient discontinuations due to adverse events with events occurring in >1 patient in any treatment group(SP583).

Adverse Event Terms	Placebo (n=283) N (%)	Fesoterodine 4mg/day (n=272) N (%)	Fesoterodine 8mg/day (n=287) N (%)	Tolterodine 4mg/day (n=290) N (%)
Prolonged QT	0 (0%)	1 (<1%)	2 (<1%)	0 (0%)
Urinary Retention	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Mucosal Dryness	0 (0%)	0 (0%)	2 (1%)	0 (0%)

Reviewer's Comments: ***In the reviewer's opinion, the reported AE's in this trial generally reflect the pharmacological activity of the compounds in this class. The safety profile of fesoterodine is not of concern, since most of the adverse events are the ones that are commonly seen with anti-muscarinic drug class.***

Patient's Assessment of Treatment Tolerance
Patients' assessment of "treatment tolerability" was collected via questionnaire at Week 12 (treatment endpoint in this study). Data for this assessment is summarized in the table below.

Appendix B. Table 8. Summary of patient responses to "Treatment Tolerability" questionnaire at Week 12 (SP583).

Tolerability Assessment	Placebo (n=283) N (%)	Fesoterodine 4mg/day (n=272) N (%)	Fesoterodine 8mg/day (n=287) N (%)	Tolterodine 4mg/day (n=290) N (%)
Excellent	99 (38%)	98 (38%)	71 (26%)	105 (38%)
Good	150 (57%)	137 (54%)	159 (58%)	150 (55%)
Moderate	11 (4%)	14 (6%)	33 (12%)	12 (4%)
Inadequate	4 (2%)	6 (2%)	13 (4%)	7 (3%)

Reviewer's Comment: ***The sponsor's contention that fesoterodine was generally well-tolerated appears to be supported by the available evidence from this trial.***

Reviewer's Safety Conclusions (for SP583):
Treatment-emergent AE's were reported in 38 % of patients in the placebo group, 50 % in the fesoterodine 4 mg group, 58 % in the fesoterodine 8 mg group, and 50 % in the tolterodine group. Most AE's were mild in intensity and the most frequently reported events were those commonly seen with agents of this class.

There was 1 death, due to myocardial infarction, in a patient that had discontinued fesoterodine 8 mg per day twenty-six (26) days earlier. This death was judged by the investigator to be not related to fesoterodine. There was another case of myocardial infarction that was reported in a patient in the tolterodine 4 mg per day group. SAE's judged by the investigator to be at least possibly related to study medication and resulted in study withdrawal were reported in a total of 8 patients.

Clinical laboratory results were consistent across all treatment groups, and no reported laboratory associated AE was seen in > 2 % in any treatment group.

There were no clinically relevant differences among treatment groups regarding vital signs, and no fesoterodine treated patients had QTc value ≥ 500 ms.

There were no clinically relevant increases in mean residual urine volumes in any treatment group (post- baseline mean values were generally < 20 mL). Residual urine volumes > 200mL were reported in 1 patient in the placebo group and 1 patient in the fesoterodine 8 mg/day group.

A total of 84-95 % of patients rated their treatment tolerance as "good" or "excellent".

Reviewer's Conclusions (for SP583):

1. Fesoterodine SR 4 and 8 mg/day for 12 weeks compared with placebo, improved the treatment response, and change in both the average number of micturitions and episodes of urge incontinence/24 hours (primary endpoints), and was generally well tolerated.
2. [redacted] b(4)
3. Prior drug treatment for OAB, age, and gender did not affect study drug efficacy in a clinically relevant manner.
4. Fesoterodine improved all measured "health outcome measure" in this trial.
5. While exploratory, comparisons between fesoterodine doses and the active control tolterodine showed no obvious differences in the primary variables in addition to the secondary efficacy and health outcome parameters measured.
6. The most frequently reported AE's were typical of antimuscarinic drugs, and were generally of mild or moderate intensity.
7. The incidence of discontinuations due to AE's was low, and ranged from 2 % for placebo to 5 % for patients in the fesoterodine 8 mg/day group.
8. Vital signs and clinical laboratory results were consistent across all treatment groups, and aside from a modest increase in heart rate, no treatment appeared to affect these parameters in a clinically relevant maner.
9. There were minor changes in ECG results, but there were no increased cardiovascular risks due to treatment observed in this trial.

Reviewer's Overall Conclusion (for SP583)

It is the opinion of this clinical reviewer that data derived from this study support the approval of fesoterodine for the treatment of OAB symptoms from both a clinical efficacy and safety viewpoint.

APPENDIX – C

Medical Officer's Review of Fesoterodine Thorough QT- Study (SP686)

NDA 22-030

Date of Submission:	**March 27, 2006**
NDA Goal Date:	**January 27, 2007**
Action Date:	**January 26, 2007**
Sponsor:	**Schwarz Biosciences, Inc.**
Drug Name:	
Referred Name:	**SPM 8272**
Proposed Name:	**Fesoterodine**
Proposed Trade Name:	[redacted] b(4)
Pharmacologic Category:	**Anti-Cholinergic (Muscarinic Receptor Antagonist)**
Study Number:	**SP686**
Development Phase:	**1**
Trial Initiation Date:	**July 30, 2004**
Trial completion Date:	**December 5, 2004**
Indication:	**Treatment of Overactive Bladder (OAB)**
Doses Used:	**4 mg & 28mg once a day**
Route of Administration	**Oral**

Protocol in Brief:
This was a double-blind, single-site, randomized, placebo- and positive-controlled, parallel-design trial of the electrocardiographic effects of 4mg and 28mg/day of fesoterodine administered orally to healthy male and female subjects. It was a "thorough QT trial".

Background:
The development of fesoterodine fumarate, a urinary antispasmodic for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency includes 4mg and 8 mg tablets. In accordance with the ICH E14 guidance (dated June 2004) and the Division's input and agreement, the Sponsor designed and conducted this thorough QT study (SP686). The trial was conducted between July 2004 and December 2004.

The following 4 different treatment arms were compared:
1) A therapeutic dose of fesoterodine (4 mg/day),
2) A supratherapeutic dose of fesoterodine (28mg/day),
3) Moxifloxacin (400mg/day) as positive control for assay sensitivity, and
4) Placebo.

In accordance with the recommendations of the Concept Paper, centrally read ECG data were analyzed by time-matched, time-averaged, and outlier analyses. Baseline values were compared with post-treatment values, and in addition, QTcF and QTcI values were correlated with fesoterodine plasma concentrations.

For purposes of designing and interpreting this TQT study, it is important to understand the basic vlinival pharmacology of fesoterodine. Following oral administration, fesoterodine is completely absorbed and rapidly de-esterified in vivo to the active metabolite **SPM 7605**. Absolute bioavailability of the active metabolite as compared to fesoterodine intravenous infusion is 52% (**SP567**). Maximum plasma levels of **SPM 7605** are achieved approximately 5 hours after administration of fesoterodine SR. Steady state is reached after 3 days and the major pathway for metabolism is via **CYP2D6**. Terminal half life of oral fesoterodine is approximately 7 hours. Hepatic metabolism and renal excretion contribute significantly to the elimination of **SPM 7605**. Approximately 70% of orally administered dose is recovered in urine as an active metabolite and 7% is recovered in the feces. he metabolites beyond SPM 7605 have low or no in vitro binding to muscarinic acetylcholine receptors. In poor metabolizers of CYP2D6, exposure to SPM 7605 was approximately doubled. Inhibition of CYP3A4 by ketoconazole resulted in an approximately 2-fold increase in exposure to SPM7605.

> ***Reviewer's Comment:*** ***Based upon the known drug-drug interactions and intrinsic metabolism variability, a dose of 28mg was deemed appropriate as the supratherapeutic dose for this TQT study by both the Clinical and Clinical Pharmacology review teams.***

Overview of Study:

Study Design:
This is a double-blind, single-site, randomized, placebo and positive-controlled, parallel design trial with oral dose administration of fesoterodine, moxifloxacin, or placebo.

Two hundred fifty-six healthy male and female subjects were assigned to 1 of the 4 parallel treatment arms (N=64 each; at least 50% female): fesoterodine 4mg/day, fesoterodine 28mg/day, moxifloxacin 400mg/day, and placebo.

For each subject, the trial consisted of an eligibility assessment (Days -28 to -3), a 6-day in-house period (Days -2 to Day 4), and a Safety follow - up visit at least 14 days after the last administration of trial medication.

Treatment Phase:
The Treatment Phase began 3 to 28 days after eligibility assessment and consisted of 3 days of treatment with fesoterodine 4mg/day or 28mg/day, 400mg/day moxifloxacin or placebo daily.

Three 12-lead electrocardiograms (ECG's) were downloaded from the ——— flash card at each of the following time points on Days -1, 1 and 3 at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 23:30 hours. Plasma samples for determination of different metabolite levels were drawn on Day 1 and Day 3 pre-dose and at 1, 2, 3, 4, 6, 8, 12, and 23:30 hours post dose. Safety and tolerability were assessed throughout the trial. b(4)

The subjects were randomized to 1 of the following 4 treatment groups:

Groups:	Treatment:
A	Fesoterodine 4mg SR tablet + 6 placebo tablets
B	Fesoterodine 4mg x 7 SR tablets
C	Moxifloxacin 400mg x 1 tablet
D	Placebo tablets x 7

Reviewer's Comment: ***The doses selected and design of this TQT study were appropriate.***

Inclusion and Exclusion Criteria:
Subjects were eligible for study participation if they were

- Healthy male or female volunteers 45-65 yrs of age
- With a body mass index (BMI) between 19 and 32 kg per m^2.
- Subjects were genotyped as extensive or poor metabolizers for cytochrome P450 2D6.
- Subjects were excluded from study participation if they presented with any of the following during screening assessments:
  * If the subjects had a history or presence of urinary retention, obstruction to bladder emptying, urethral stricture or BPH.
  * Resting heart rate < 50 bpm or > 100bpm.
  * Systolic blood pressure <100 mm Hg or >160mm Hg or a diastolic blood pressure >95 mmHg.
  *Any clinically relevant changes in ECG, such as conduction abnormalities, or QRS prolongation.

Reviewer's Comment: ***Both inclusion and exclusion criteria were adequate.***

Study Endpoints:
The primary endpoint in this study was the change from baseline in QTcF (Fridericia correction).

Secondary endpoints in this study included: change from baseline in QTc based on individual and Bazette correction methods, and change from baseline in heart rate, PR interval, QRS interval, ECG morphological patterns and uncorrected QT interval.

Reviewer's Comment: ***Both primary and secondary endpoints selected for this study were appropriate.***

Safety Evaluations:
Safety and tolerability assessments included the monitoring and recording of all adverse events, vital signs, laboratory data (biochemistry, hematology and urinalysis), physical examinations and ECG tracings.

ECG Recordings:
ECG's were obtained digitally using a [redacted] ECG continuous recorder. The ECGs were stored on a flashcard about every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed. ECG's used in the analysis were selected by pre-determined time points and read centrally using a high-resolution manual on-screen caliper method with annotations, thereby meeting the highest standard described in the recent ICH Steering Committee Draft Consensus Guideline dated 10 June 2004. b(4)

ECG interval and morphology changes were based on change from baseline, where the baseline was the mean of the 36 recordings obtained on Day -1. Three 12-lead ECGs were downloaded from the [redacted] flashcard within 1 minute (providing 3 ECGs for each time point) at baseline (Day –1), Day 1, and Day 3 at the following time points from dosing in all 4 groups: 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 23:30 hours. b(4)

A total of 36 ECGs were analyzed at baseline for each subject to construct an "individual" QT correction. If these 36 ECG measurements at baseline could not adequately construct an individual QT correction, more baseline ECGs were retrospectively retrieved from the [redacted] flashcard to provide an accurate individual QT correction. However, only the original 36 ECGs were used to establish the baseline ECG interval value. b(4)

In addition to the 36 Baseline ECGs, 36 ECGs were analyzed on Day 1 and Day 3, resulting in a total of 108 ECG's per subject. This provided a total of 27,648 ECG's with 256 subjects completing the treatment phase of the trial.

Safety Results From the TQT Study

Clinical Adverse Events:
All subjects who completed the trial (256 subjects) received all assigned doses of trial medication for the duration of 3 days. Five subjects (1 in the placebo group and 4 in the

fesoterodine 28mg/day group) discontinued from the trial after 1 day of treatment with trial medication.

Overall, headache and rash were the most frequently reported AE's experienced by 5.4% (14/261) and 7.3% (19/261) subjects respectively among all treatment groups combined. The incidence of these AE's was comparable across treatment groups with 6.2%, 6.3%, 5.9%, and 3.1% of subjects experiencing headache and 4.6%, 6.3%, 7.4%, and 10.9% of subjects experiencing rash in the placebo, 4mg/day fesoterodine, 28mg/day fesoterodine, and moxifloxacin treatment groups, respectively. Most of the cases of rash were reported as being the result of reactions to the ECG lead placement.

> ***Reviewer's Comment: It is not unusual to see localized skin rash secondary to placement of ECG leads superficially across chest and limbs. This does not raise a new concern for fesoterodine.***

Adverse events were most frequently experienced by subjects in fesoterodine 28mg/day treatment group and consisted primarily of expected anti-muscarinic effects. The most common AE's in the 28mg/day fesoterodine group were abdominal pain and constipation (8.8% each), rash (7.4%), headache (5.9%), and mouth dry, vomiting, pharyngitis, and urinary retention (4.4% each). Adverse events experienced by subjects in the fesoterodine treatment groups (except for one case of conjunctival hemorrhage), were consistent with those seen in other drug trials with prominent anti-muscarinic drug effects.

The clinical adverse events in this TQT trial are summarized in the table below.

Appendix C. Table 1.

Summary of subjects with treatment-emergent adverse events during treatment (SS in SP686)

Body system Preferred term	Placebo N=65	Feso 4mg/day N=64	Feso 28mg/day N=68	Moxi N=64	All subjects N=261
	n (%)				
Any body system Any event	9 (13.8)	9 (14.1)	26 (38.2)	12 (18.8)	56 (21.5)
Autonomic nervous system disorders	0	0	3 (4.4)	1 (1.6)	4 (1.5)
Mouth dry	0	0	3 (4.4)	0	3 (1.1)
Palpitation	0	0	0	1 (1.6)	1 (0.4)
Body as a whole – general disorders	4 (6.2)	4 (6.3)	4 (5.9)	3 (4.7)	15 (5.7)
Headache	4 (6.2)	4 (6.3)	4 (5.9)	2 (3.1)	14 (5.4)
Fatigue	0	0	0	1 (1.6)	1 (0.4)
Central and peripheral nervous system disorders	0	1 (1.6)	1 (1.5)	1 (1.6)	3 (1.1)
Dizziness	0	1 (1.6)	1 (1.5)	1 (1.6)	3 (1.1)
Gastrointestinal system disorders	1 (1.5)	0	12 (17.6)	2 (3.1)	15 (5.7)
Abdominal pain	0	0	6 (8.8)	0	6 (2.3)
Constipation	0	0	6 (8.8)	0	6 (2.3)
Vomiting	0	0	3 (4.4)	1 (1.6)	4 (1.5)
Dyspepsia	0	0	1 (1.5)	1 (1.6)	2 (0.8)
Diarrhea	1 (1.5)	0	0	1 (1.6)	2 (0.8)
Nausea	0	0	0	1 (1.6)	1 (0.4)
Musculo-skeletal system disorders	2 (3.1)	1 (1.6)	0	1 (1.6)	4 (1.5)
Back pain	2 (3.1)	1 (1.6)	0	1 (1.6)	4 (1.5)
Respiratory system disorders	0	0	3 (4.4)	0	3 (1.1)
Pharyngitis	0	0	3 (4.4)	0	3 (1.1)
Skin and appendages disorders	3 (4.6)	4 (6.3)	5 (7.4)	8 (12.5)	20 (7.7)
Rash	3 (4.6)	4 (6.3)	5 (7.4)	7 (10.9)	19 (7.3)
Rash erythematous	0	0	0	1 (1.6)	1 (0.4)
Urinary system disorders	0	0	4 (5.9)	0	4 (1.5)
Urinary retention	0	0	3 (4.4)	0	3 (1.1)
Dysuria	0	0	1 (1.5)	0	1 (0.4)
Vision disorders	0	0	1 (1.5)	0	1 (0.4)
Conjunctival hemorrhage	0	0	1 (1.5)	0	1 (0.4)

Almost all AE's were mild in intensity (100/107 events) except for two subjects who had events that were severe in intensity. **Subject # 80160** in the fesoterodine 28mg/day group experienced severe urinary retention which was relieved by simple catheterization and involved no further medical intervention. The second **subject # 80508,** who was in the moxifloxacin group, had 3 severe AE's, i.e. leg pain, arthralgia, and accident not otherwise specified (NOS). None of these events required any further clinical workup.

> ***Reviewer's Comment:*** ***Although one subject in the supratherapeutic dose group experienced urinary retention, it was mild in intensity and was promptly relieved by catheterization. Urinary retention is a common adverse event seen with most of the anti-cholinergic/muscarinic drugs. The other subject who had non-specific adverse events (mild in intensity) required no further medical intervention as reported by the sponsor.***

Discontinuations due to Adverse Events (AEs):
Two subjects discontinued from this trial due to AEs:

Subject 80129, a 65-year-old female discontinued from the trial following the AEs of dry mouth and pharyngitis that was reported on Day 1. Both events were mild in intensity. The dry mouth was judged by the investigator to be possibly related to trial medication and the pharyngitis was judged by the investigator as not related to the trial medication. Both events resolved in 5 days.

Subject 80160, a 59-year-old male discontinued from the trial following an AE of urinary retention reported on Day 1. The subject required catheterization to relieve his urinary retention. The event was severe in intensity and judged by the investigator to be probably related to trial medication. The event was resolved in 3 days.

Deaths:
No deaths were reported in this trial.

Serious Adverse Events (SAEs):
One subject experienced an SAE during the trial. **Subject # 80508,** a 63-year-old female in the moxifloxacin treatment group, had an accident NOS (fractured her left foot) on the day after her last dose of trial medication. The SAE was not considered related to the trial medication and the subject recovered fully 40 days after the event occurred.

Other Medically Significant Adverse Events:
Two subjects reported palpitations. **Subject # 80150,** a 63-year-old male in the placebo group reported palpitations 2 days following the last dose of trial medication that lasted for a day. The event was mild in intensity, judged to be possibly related to trial medication by the investigator. **Subject # 80564**, a 50-year-old female in the moxifloxacin group reported palpitations on Day 3 of the trial. The event was mild in intensity and was judged to be possibly related to trial medication by the investigator and continued for 2 days.

Three subjects reported dizziness. **Subject # 80202**, a 53-year-old male in the 4mg/day fesoterodine group, reported dizziness on Day 3 of the trial which lasted for 1 day. The event was mild in the intensity and was judged to be possibly related to trial medication by the investigator. **Subject # 80552**, a 55-year-old female in the 28mg/day fesoterodine group reported dizziness on Day 2 of the trial. The event was mild in intensity and was judged to be possibly related to trial medication by the investigator and lasted for 16 days. **Subject # 80575**, a 60-year-old female in the moxifloxacin group reported dizziness on Day 3 of the trial. The event was mild in intensity and was judged to be probably related to trial medication by the investigator and lasted for 2 days.

None of the adverse events of palpitations or dizziness resulted in any modification of trial medication and all events were resolved without any further medical/critical intervention.

Appendix C. Table 2. Summary of adverse events of palpitation or dizziness in the thorough QT study, by treatment group.

Event	Placebo N=65	Feso 4mg N=64	Feso 28mg N=68	Moxi N=64	Total N=261
Palpitations	1 (1.5%)	0	0	1 (1.6%)	2 (0.8%)
Dizziness	0	1 (1.6%)	1 (1.5%)	1 (1.6%)	3 (1.1%)

Reviewer's Comments: ***The reviewer points out that there were no serious adverse events that occurred during this trial except for one subject in the moxifloxacin group who experienced a fractured left foot following the last dose of the medication that according to this clinical reviewer could not be related to the trial medication.***

However, there was one subject, who discontinued from the trial because of urinary retention that required simple catheterization.

There were no cases of pro-arrhythmic potential other than one case of palpitation each in the moxifloxacin and placebo groups and three cases of dizziness (one each in fesoterodine groups) and one in moxifloxacin group. Both the events were mild in intensity and required no medical intervention.

Electrocardiographic Assessment Results:

In the placebo, fesoterodine 4mg/day, and fesoterodine 28mg/day treatment groups, there was a decrease in the mean QTcF from baseline of -4.3, -5.0 and -7.0 ms, respectively on Day 1; and -4.7, -4.6 and -5.0 ms, respectively on Day 3. The positive control (moxifloxacin) showed the expected increase from baseline in QTcF: 4.9ms on Day 1 and 8.6ms on Day 3.

The following tables summarize the results for the primary variable: change from baseline in QTc using the Fridericia correction method.

Appendix C. Table 3: Summary results for QTcF (Baseline, Day 1 & Day 3) by treatment group.

Treatment Group	Day	n	Mean (SD)	Median	Range (Min, Max)	95% CI
Observed value (ms)						
Placebo (N=65)	Baseline	65	403.6 (17.07)	402.1	370.5, 444.8	
	Day 1	65	399.3 (16.02)	398.6	364.7, 438.2	
	Day 3	64	399.1 (16.50)	397.6	360.8, 434.2	
Feso 4mg/day (N=64)	Baseline	64	408.5 (16.25)	409.1	369.7, 444.4	
	Day 1	64	403.5 (16.83)	403.4	368.4, 464.3	
	Day 3	64	403.9 (14.18)	403.9	373.7, 433.8	
Feso 28mg/day (N=68)	Baseline	68	404.5 (16.68)	403.2	375.0, 458.5	
	Day 1	68	397.4 (13.25)	395.4	370.9, 430.6	
	Day 3	64	400.1 (14.02)	400.8	370.1, 440.6	
Moxifloxacin (N=64)	Baseline	64	400.6 (15.60)	400.9	365.7, 444.3	
	Day 1	64	405.4 (16.17)	405.5	370.5, 459.6	
	Day 3	64	409.1 (16.70)	410.4	375.4, 462.1	
Change from Baseline (ms)						
Placebo (N=65)	Day 1	65	-4.3 (5.26)	-4.2	-19.0, 7.5	(-5.6, -3.0)
	Day 3	64	-4.7 (5.89)	-3.8	-20.2, 11.6	(-6.2, -3.2)
Feso 4mg/day (N=64)	Day 1	64	-5.0 (9.86)	-6.0	-18.4, 58.9	(-7.5, -2.6)
	Day 3	64	-4.6 (6.71)	-4.9	-18.5, 11.9	(-6.3, -2.9)
Feso 28mg/day (N=68)	Day 1	68	-7.0 (7.20)	-6.0	-27.9, 10.8	(-8.8, -5.3)
	Day 3	64	-5.0 (7.85)	-5.3	-20.8, 16.3	(-6.9, -3.0)
Moxifloxacin (N=64)	Day 1	64	4.9 (5.79)	4.8	-8.4, 15.4	(3.4, 6.3)
	Day 3	64	8.6 (5.94)	7.7	-2.7, 21.2	(7.1, 10.1)

Appendix C. Table 4. Summary analyses of change-from-baseline in QTcF (at Day 1 & Day 3), by treatment group.

Treatment	n	Endpoint LSMean	Comparison	Treatment Difference (SE)	p-value	95% CI
Day 1						
Placebo	65	-4.6	4mg vs Pbo	0.0 (1.20)	0.978	(-2.3, 2.4)
Feso 4mg/day	64	-4.6	28mg vs Pbo	-2.7 (1.17)	0.022	(-5.0, -0.4)
Feso 28mg/day	68	-7.3	Moxi vs Pbo	8.6 (1.19)	<0.001	(6.3, 11.0)
Moxifloxacin	64	4.0	28mg vs 4mg	-2.7 (1.18)	0.022	(-5.1, -0.4)
			4mg vs Moxi	-8.6 (1.21)	<0.001	(-11.0, -6.2)
			28mg vs Moxi	-11.3 (1.18)	<0.001	(-13.6, -9.0)
Day 3						
Placebo	64	-5.1	4mg vs Pbo	0.8 (1.09)	0.452	(-1.3, 3.0)
Feso 4mg/day	64	-4.2	28mg vs Pbo	-0.1 (1.09)	0.895	(-2.3, 2.0)
Feso 28mg/day	64	-5.2	Moxi vs Pbo	12.7 (1.09)	<0.001	(10.6, 14.8)
Moxifloxacin	64	7.6	28mg vs 4mg	-1.0 (1.09)	0.376	(-3.1, 1.2)
			4mg vs Moxi	-11.9 (1.10)	<0.001	(-14.0, -9.7)
			28mg vs Moxi	-12.8 (1.09)	<0.001	(-15.0, -10.7)

These tables of results demonstrate that were no significant differences in the change from baseline in QTcF on Day 3 between the fesoterodine treatment groups and the placebo group. The change from baseline in QTcF on Day 1 was not significantly different between the 4mg/day fesoterodine group and placebo (p=0.978); the reduction in QTcF from baseline at Day 1 was statistically significant and more pronounced in fesoterodine 28mg/day group than in the placebo and fesoterodine 4mg/day groups (p=0.022 for each difference). The change from baseline in QTcF following treatment with moxifloxacin was statistically significant and greater than other three treatment groups (p<0.001) at both Day 1 and Day 3, as expected.

While the primary endpoint was change-from-baseline in QTc using the Fridericia correction method, the data was analyzed using other corrections methods. The following table shows the data using the individualized correction method.

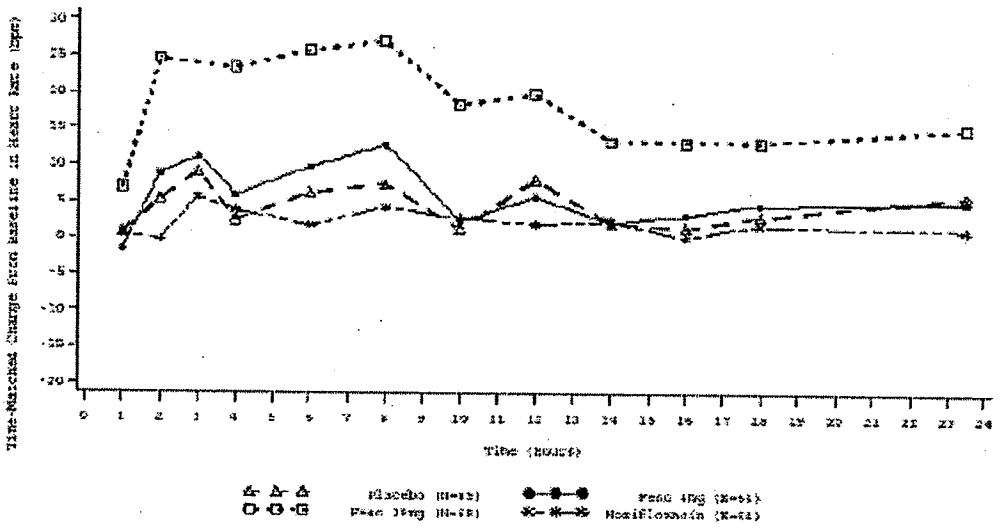
Appendix C. Table 5. Summary analyses of change-from-baseline in QTcI (Day 1 & Day 3), by treatment group.

Treatment	n	Endpoint LSMean	Comparison	Treatment Difference (SE)	p-value	95% CI
Day 1						
Placebo	65	-4.4	4mg vs Pbo	-1.1 (1.64)	0.485	(-4.4, 2.1)
Feso 4mg/day	64	-5.6	28mg vs Pbo	-5.0 (1.61)	0.002	(-8.2, -1.8)
Feso 28mg/day	68	-9.5	Moxi vs Pbo	8.1 (1.64)	<0.001	(4.9, 11.4)
Moxifloxacin	64	3.7	28mg vs 4mg	-3.9 (1.62)	0.018	(-7.1, -0.7)
			4mg vs Moxi	-9.3 (1.66)	<0.001	(-12.5, -6.0)
			28mg vs Moxi	-13.2 (1.62)	<0.001	(-16.3, -10.0)
Day 3						
Placebo	64	-5.2	4mg vs Pbo	-0.2 (1.55)	0.875	(-3.3, 2.8)
Feso 4mg/day	64	-5.5	28mg vs Pbo	-2.1 (1.54)	0.175	(-5.1, 0.9)
Feso 28mg/day	64	-7.3	Moxi vs Pbo	12.5 (1.55)	<0.001	(9.4, 15.5)
Moxifloxacin	64	7.2	28mg vs 4mg	-1.9 (1.55)	0.232	(-4.9, 1.2)
			4mg vs Moxi	-12.7 (1.56)	<0.001	(-15.8, -9.7)
			28mg vs Moxi	-14.6 (1.55)	<0.001	(-17.6, -11.5)

The overall changes observed during QTCI analysis were similar to those for QTcF. A summary of changes from baseline at Day 1 and Day 3 for heart rate, PR interval, QRS duration, QT interval, and QTcB interval as submitted by the sponsor are as follows: There were no notable differences between treatment groups in the absolute values and changes from baseline on Day 1 or Day 3 in the PR interval or the QRS duration. The results for the uncorrected QT interval were similar to those seen for the QTcF and QTcI interval, although the decrease in the uncorrected QT interval following treatment with fesoterodine 28mg/day was more pronounced on Day 1 and Day 3 than was seen with the QTcF or QTcI interval. This was expected due to the anti-muscarinic effect of fesoterodine on heart rate. The following figures show heart rate changes from baseline to Days 1 and 3 respectively.

Appendix C. Figure 1.

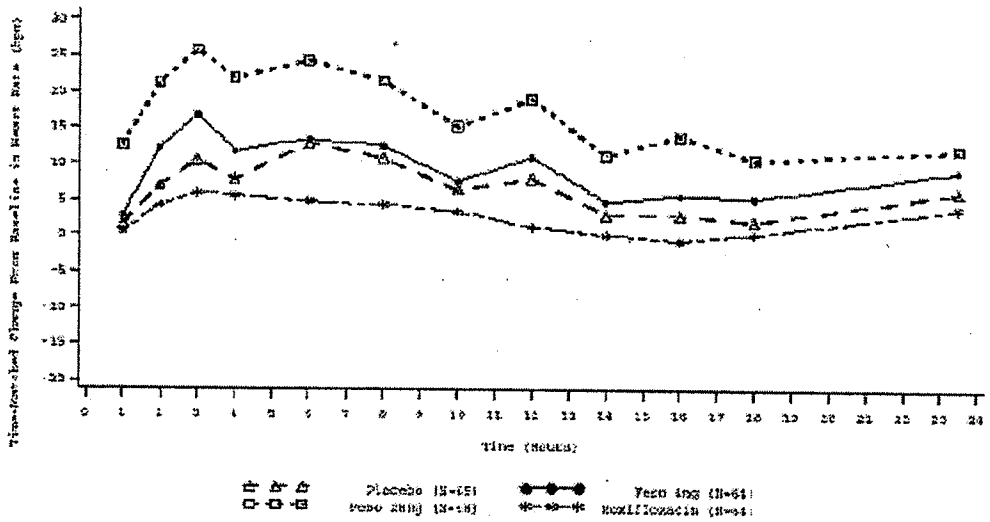
Change from Baseline in heart rate on Day 1 (PDS in SP686)



Appears This Way
On Original

Appendix C. Figure 2.

Change from Baseline in heart rate on Day 3 (PDS in SP686)



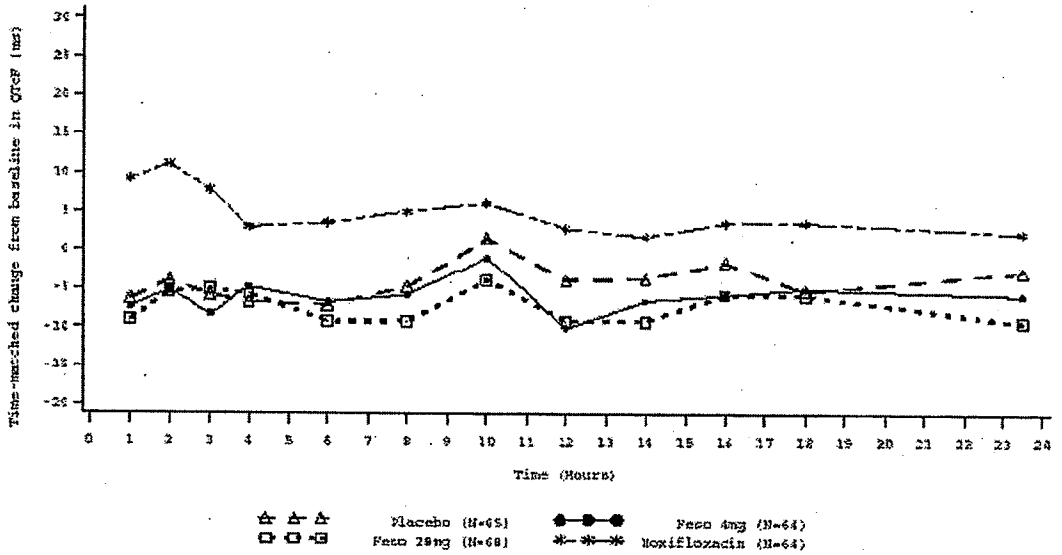
It is evident from the graphs plotted above that there a change in heart rate from baseline on Day 1 and Day 3. The change demonstrates an increase in the heart rate from baseline at Day 1 and Day 3 for both fesoterodine 4mg/day and 28mg/day treatment groups and the effect was more clearly pronounced in the 28mg/day group. The ability to increase heart rate is a known effect of anti-muscarinic drugs, including fesoterodine.

> ***Reviewer's Comment:*** ***This reviewer acknowledges the fact that almost all anti-muscarinic drugs are associated with an increase in the heart rate. Therefore, it comes as no surprise that fesoterodine is associated with a mild increase in the heart rate. The effect being slightly more pronounced in subjects treated with fesoterodine 28mg.***

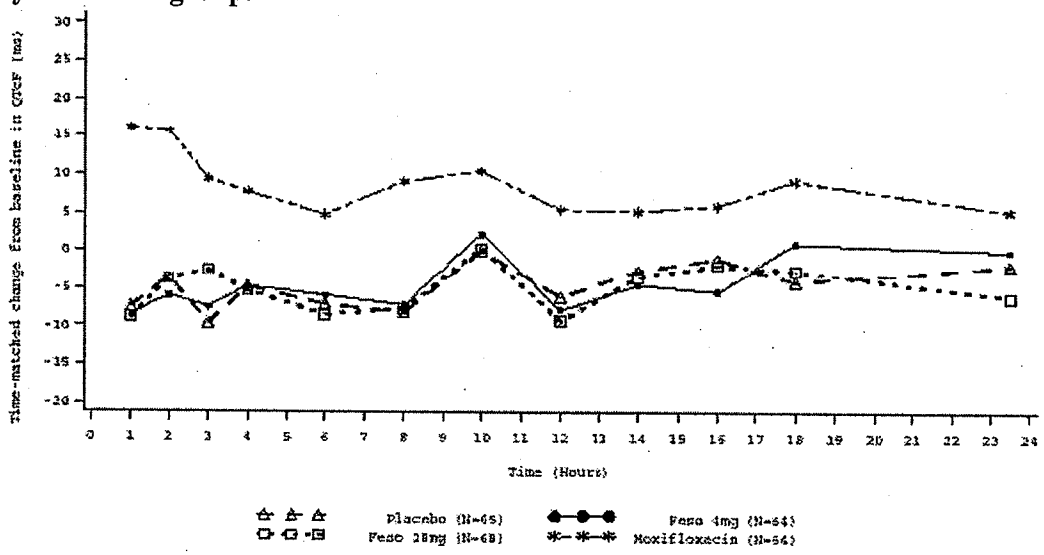
An additional analysis was conducted to assess the effect of fesoterodine on the QT interval during the day versus at night. The results for this analyses are shown graphically for Days 1 and 3 in the next two figures.

Appears This Way
On Original

Appendix C. Figure 3. **Nocturnal variation from baseline for QTcF (on Day 1), by treatment group.**



Appendix C. Figure 4. **Nocturnal variation from baseline for QTcF (on Day 3), by treatment group.**



The results for this analysis showed an increase in QTcF during the night at baseline and on Days 1 and 3. However, the mean changes from baseline did not show any systemic day/night effects. These results were similar for uncorrected QT. There was less day/night fluctuation seen in QTcB, possibly because the effects were offset by the decreased heart rate during rest at night.

As expected, there was a lower heart rate during the night in all treatment groups at baseline, Day 1, and Day 3. There were no notable fluctuations in the other ECG parameters (PR interval, QRS duration) throughout the day.

> ***Reviewer's Comment:*** ***According to this clinical reviewer, the change in QTcF during the night hours is minimal, ranging from – 4ms to 2ms. This change is not medically significant and understandable in view of the fact that the heart rate is slower during night hours.***

Another analysis was conducted to assess the greatest (maximum) change in QTcF. The results from this analysis are presented in the next two tables.

A summary of the maximum change in QTcF and summary analyses are presented in the following tables:

Appendix C. Table 6: Summary of the maximum change in QTcF (ms), by treatment group.

Treatment Group	n	Mean (SD)	Median	Range (Min, Max)	95% CI
Placebo	65	21.4 (8.94)	20.3	4.0, 55.7	(19.2, 23.6)
Feso 4mg/day	64	20.3 (11.31)	18.8	1.0, 53.7	(17.5, 23.1)
Feso 28mg/day	68	19.3 (9.69)	18.0	-3.7, 43.7	(16.9, 21.6)
Moxifloxacin	64	32.2 (9.96)	30.0	19.0, 67.7	(29.7, 34.7)

Appendix C. Table 6: Summary analyses of the maximum change in QTcF (ms), by treatment group.

Treatment	n	Endpoint LSMean	Comparison	Treatment Difference (SE)	p-value	95% CI
Placebo	65	21.1	4mg vs Pbo	-0.5 (1.68)	0.749	(-3.8, 2.8)
Feso 4mg/day	64	20.5	28mg vs Pbo	-2.5 (1.65)	0.124	(-5.8, 0.7)
Feso 28mg/day	68	18.5	Moxi vs Pbo	10.2 (1.67)	<0.001	(6.9, 13.5)
Moxifloxacin	64	31.3	28mg vs 4mg	-2.0 (1.66)	0.229	(-5.3, 1.3)
			4mg vs Moxi	-10.7 (1.69)	<0.001	(-14.1, -7.4)
			28mg vs Moxi	-12.7 (1.65)	<0.001	(-16.0, -9.5)

The data in these tables shows no statistically significant differences in the maximum change in QTcF between the placebo group and either the 4mg/day fesoterodine group (p=0.749) or the 28mg/day fesoterodine group (p=0.124). Also, there was no statistically significant difference between the two fesoterodine dose groups (p=0.229). The maximum change in QTcF was statistically significant larger following treatment with moxifloxacin than in any of the other treatment groups (p<0.001). The 95% CI for the maximum change in QTcF following treatment with moxifloxacin did not overlap with the 95% CI for the maximum change following treatment with fesoterodine or placebo.

Additional analyses were conducted using pre-defined categorical cutpoints for absolute corrected QT interval and changes-from-baseline in the corrected QT interval. These data are presented in the next two tables.

Appendix C. Table 7: Summary of subjects with pre-defined absolute QT or corrected QT intervals, using all 3 corrections methods, and by treatment group.

Parameter	Placebo N=65	Feso 4mg/day N=64	Feso 28mg/day N=68	Moxi N=64
	n (%)			
QTcF				
QTcF >450ms	3 (4.6)	2 (3.1)	0	7 (10.9)
QTcF >480ms	0	0	0	0
QTcF >500ms	0	0	0	0
QTcI				
QTcI >450ms	4 (6.2)	5 (7.8)	2 (2.9)	8 (12.5)
QTcI >480ms	2 (3.1)	1 (1.6)	0	0
QTcI >500ms	0	0	0	0
Uncorrected QT				
QT >450ms	3 (4.6)	0	0	4 (6.3)
QT >480ms	1 (1.6)	0	0	1 (1.6)
QT >500ms	0	0	0	0
QTcB				
QTcB >450ms	9 (13.8)	15 (23.4)	20 (29.4)	25 (39.1)
QTcB >480ms	0	2 (3.2)	1 (1.5)	5 (7.8)
QTcB >500ms	0	0	0	0

The data in the preceding table show no [redacted] ECG's with a QTcF, QTcI, QTcB, or uncorrected QT value of 500ms or greater at any post-baseline time point that were not present at baseline. No subject had a new onset QTcF value >480ms. The percentage of subjects with new onset values for QTcF of >450ms was 4.6, 3.1, 0, and 10.9 in the placebo, 4mg/day fesoterodine, 28mg/day fesoterodine, and moxifloxacin groups, respectively. The new onset values in QTcF that were >450ms in the 4mg/day fesoterodine group represented 1 occurrence each in 2 subjects.

b(4)

The percentage of subjects with new onset QTcI values of >450ms was 6.2, 7.8, 2.9 and 12.5 in the placebo group, fesoterodine 4mg/day and 28mg/day groups and moxifloxacin group, respectively. Two subjects in the placebo group and 1 subject in the fesoterodine 4mg/day group had new onset QTcI values that were >480ms. Subject 80122, in the 4mg/day fesoterodine group had a QTcI of 488.5ms on Day 1. Most of these represented isolated instances. However, Subject 80196 in fesoterodine 28mg/day group had 7 instances of new onset QTcI >450ms (ranging from 454.0 to 478.4ms) on Days 1 and Day 3. This subject had no values for QTcF on Day 1 or Day 3 that exceeded 450ms.

No subject in either of the fesoterodine treatment groups had a new onset uncorrected QT value that was >450ms. Two (3.2%) subjects in fesoterodine 4mg/day group, 1 (1.5%) subject in fesoterodine 28mg/day group and 5 (7.8%) subjects in the moxifloxacin group had new onset QTcB values >480ms. Nine (13.8%) subjects in the placebo group, 15 (23.4%) subjects in the 4mg/day fesoterodine group, 20 (29.4%) subjects in the 28mg/day

fesoterodine group, and 25 (39.1%) subjects in the moxifloxacin group had new onset QTcB values that were >450ms.

***Reviewer's Comment**: The higher percentages of subjects with increases in QTcB in the fesoterodine treatment groups than in the placebo group is due to the increase in heart rate following treatment with fesoterodine.*

Appendix C. Table 8: Summary of subjects with pre-defined changes-from-baseline in absolute QT, corrected QT intervals using all 3 corrections methods, and other EKG intervals, and by treatment group.

Parameter	Placebo N=65	Feso 4mg/day N=64	Feso 28mg/day N=68	Moxi N=64
	n (%)			
QTcF				
Increase of QTcF 30 to <60ms	10 (15.4)	12 (18.8)	12 (17.6)	32 (50.0)
Increase of QTcF ≥60ms	0	0	0	1 (1.6)
QTcI				
Increase of QTcI 30 to <60ms	7 (10.8)	8 (12.5)	11 (16.2)	31 (48.4)
Increase of QTcI ≥60ms	0	1 (1.6)	1 (1.5)	1 (1.6)
Uncorrected QT				
Increase of QT 30 to <60ms	27 (41.5)	16 (25.0)	6 (8.8)	52 (81.3)
Increase of QT ≥60ms	0	3 (4.7)	0	12 (18.8)
QTcB				
Increase of QTcB 30 to <60ms	39 (60.0)	36 (56.3)	55 (80.9)	56 (87.5)
Increase of QTcB ≥60ms	1 (1.5)	4 (6.3)	8 (11.8)	6 (9.4)
Heart rate				
Decrease >25% and <50bpm	1 (1.5)	0	0	0
Increase >25% and >100bpm	11 (16.9)	25 (39.1)	52 (76.5)	15 (23.4)
PR interval				
Increase >25% and >200ms	1 (1.5)	0	0	1 (1.6)
QRS duration				
Increase >25% and >100ms	0	1 (1.6)	0	0

The data in the preceding table shows that one subject (# **80524)** in the moxifloxacin treatment group had a change from baseline of ≥60ms in the QTcF interval at Day 3, Hour 1. No other subject had a change from baseline in QTcF that was 60ms or greater at any time point during the trial. Three subjects, 1 each in the 4mg/day, 28mg/day fesoterodine, and moxifloxacin treatment groups had an increase from baseline in the QTcI interval that was ≥60ms. Three subjects in the 4mg/day fesoterodine group and 12 subjects in the moxifloxacin group had increases from baseline in the uncorrected QT that were ≥60ms.

The percentage of subjects with increases in QTcF that were 30 to 60ms was higher in the moxifloxacin group, 51.6% compared with 15.4%, 18.8%, and 17.6% in the placebo, 4mg/day fesoterodine, and 28mg/day fesoterodine groups, respectively. These results were similar with QTcI.

The percentage of subjects with increases in the uncorrected QT interval that were 30 to 60ms was also higher in the moxifloxacin group; however, this percentage was lower in the fesoterodine treatment groups than placebo, as expected due to the anti-muscarinic

action of fesoterodine (41.5%, 25.0%, and 8.8% in the placebo, 4mg/day fesoterodine, and 28mg/day fesoterodine groups, respectively), which can be explained by the increased heart rates in the fesoterodine treatment groups. In contrast, the percentage of subjects with increases in QTcB that were 30 to 60ms was higher in both the moxifloxacin group and the 28mg/day fesoterodine group (87.5% and 80.9%, respectively) compared with the placebo and 4mg/day groups (60.0% and 56.3%, respectively), which is also due to the increase in heart rate following treatment with fesoterodine.

Only 1 subject, in the placebo group, had a decrease in heart rate that met the outlier criteria.

> ***Reviewer's Comment: As expected, the percentage of subjects with increases in heart rate that met the outlier criteria was higher in the fesoterodine groups.***

Two subjects had increase in the PR interval that met the outlier criteria. Subject 80535, in the placebo group, had 1 increase in the PR interval that met the outlier criteria and Subject 80508, in the moxifloxacin group, had 5 increases in PR interval that met outlier criteria.

Subject 80149, in the 4mg/day fesoterodine group, had an increase in the QRS duration to 101.7ms on Day 3 (at Hour 3).

The electrocardiograms from this trial were further analyzed for all possible morphological abnormalities. The results of this analysis are shown in the next table.

No subject had a myocardial infarction and/or abnormal U wave finding during this trial. In general, the number of subjects who had an abnormal ECG finding was similar at baseline and post-baseline for all treatment groups and was similar across the treatment groups, except for sinus bradycardia and tachycardia. In the fesoterodine treatment groups, there was an increase in the number of subjects with sinus tachycardia and a corresponding decrease in the number of subjects with sinus bradycardia following treatment.

> ***Reviewer's Comment: Sinus tachycardia is not an unexpected ECG finding in this study due to the antimuscarinic effects of fesoterodine on heart rate, especially at the supratherapeutic dose.***

Appendix C. Table 9. Summary of all ECG morphological changes, by treatment group.

CATEGORY Finding Visit	Placebo N=65	Feso 4mg/day N=64	Feso 28mg/day N=68	Moxi N=64
	n/N (%)[a]			
ARRHYTHMIA				
Atrial premature complexes				
Baseline	0/65	0/64	0/68	1/64 (1.6)
Post-Baseline	1/65 (1.5)	1/64 (1.6)	0/68	0/63
Ventricular premature complexes				
Baseline	1/65 (1.5)	0/64	0/68	0/64
Post-Baseline	1/64 (1.6)	1/64 (1.6)	1/68 (1.5)	0/64
RHYTHM				
Ectopic supracentricular rhythm				
Baseline	2/65 (3.1)	0/64	1/68 (1.5)	0/64
Post-Baseline	0/63	0/64	0/67	0/64
Sinus bradycardia				
Baseline	7/65 (10.8)	11/64 (17.2)	11/68 (16.2)	5/64 (7.8)
Post-Baseline	1/58 (1.7)	0/53	0/57	0/59
Sinus tachycardia				
Baseline	8/65 (12.3)	10/64 (15.6)	10/68 (14.7)	18/64 (28.1)
Post-Baseline	24/57 (42.1)	32/54 (59.3)	49/58 (84.5)	13/46 (28.3)
CONDUCTION				
First degree AV block				
Baseline	5/65 (7.7)	4/64 (6.3)	3/68 (4.4)	4/64 (6.3)
Post-Baseline	3/60 (5.0)	2/60 (3.3)	2/65 (3.1)	2/60 (3.3)
Intraventricular conduction defect				
Baseline	4/65 (6.2)	8/64 (12.5)	9/68 (13.2)	7/64 (10.9)
Post-Baseline	2/61 (3.3)	2/56 (3.6)	3/59 (5.1)	2/57 (3.5)
Left anterior hemiblock				
Baseline	3/65 (4.6)	4/64 (6.3)	7/68 (10.3)	0/64
Post-Baseline	1/62 (1.6)	2/60 (3.3)	3/61 (4.9)	1/64 (1.6)
Prolonged QTc[b]				
Baseline	3/65 (4.6)	2/64 (3.1)	1/68 (1.5)	2/64 (3.1)
Post-Baseline	3/62 (4.8)	2/62 (3.2)	1/67 (1.5)	1/62 (1.6)
Right bundle branch block				
Baseline	0/65	0/64	0/68	0/64
Post-Baseline	0/65	0/64	1/68 (1.5)	0/64

Appendix C. Table 9 (continued). Summary of all ECG morphological changes, by treatment group.

CATEGORY Finding Visit	Placebo N=65	Feso 4mg/day N=64	Feso 28mg/day N=68	Moxi N=64
	n/N (%)[a]			
MORPHOLOGY				
Low voltage				
Baseline	1/65 (1.5)	0/64	0/68	0/64
Post-Baseline	2/64 (3.1)	1/64 (1.6)	2/68 (2.9)	1/64 (1.6)
ST SEGMENT				
Depressed				
Baseline	1/65 (1.5)	0/64	1/68 (1.5)	1/64 (1.6)
Post-Baseline	0/64	0/64	4/67 (6.0)	1/63 (1.6)
Elevated				
Baseline	0/65	0/64	0/68	0/64
Post-Baseline	0/65	0/64	0/68	1/64 (1.6)
T WAVES				
Biphasic				
Baseline	4/65 (6.2)	4/64 (6.3)	8/68 (11.8)	5/64 (7.8)
Post-Baseline	4/61 (6.6)	7/60 (11.7)	7/60 (11.7)	4/59 (6.8)
Flat				
Baseline	22/65 (33.8)	17/64 (26.6)	25/68 (36.8)	19/64 (29.7)
Post-Baseline	8/43 (18.6)	12/47 (25.5)	17/43 (39.5)	8/45 (17.8)
Inverted				
Baseline	7/65 (10.8)	4/64 (6.3)	12/68 (17.6)	4/64 (6.3)
Post-Baseline	6/58 (10.3)	10/60 (16.7)	4/56 (7.1)	8/60 (13.3)

Conclusions from the Electrocardiographic (EKG) Assessments:

• Both time-averaged and time-matched assessments showed an overall negative mean change from baseline in QTcF following dosing with either fesoterodine 4mg (therapeutic range) or fesoterodine 28mg (supra-therapeutic range) on both Day 1 and Day 3. The magnitude of the decrease was similar to that seen following treatment with placebo. Assay sensitivity was shown by an increase from baseline in QTcF following treatment with moxifloxacin. Similar results were seen for QTcI.

• Data from outlier analysis were consistent with the absence of any QT prolongation effect associated with treatment with fesoterodine. There were no notable differences in the number of QTcF outliers between placebo and either of the fesoterodine treatment groups. In contrast, there was a higher incidence of QTcF outliers following treatment with moxifloxacin.

• In general, the number of outliers for other ECG parameters was similar across treatment groups. The exception was for heart rate in which case the number of outliers was higher in the fesoterodine treatment groups due to the pharmacologic effect of anti-cholinergics to increase heart rate.

• No effects of fesoterodine on ECG morphology were noted.

Summary of EKG Conclusions For SP686 (the Thorough QT Study)

This trial was conducted in order to investigate potential electrocardiographic effects of fesoterodine at steady state after administration of a therapeutic (4mg/day) dose and supra-therapeutic (28mg/day) dose for 3 days. Additionally, the correlation between plasma concentration of fesoterodine (**SPM 7605**) and the QT interval was examined and the safety and tolerability of the treatment was evaluated.

This trial demonstrated that fesoterodine following a therapeutic dose (4mg) or a supratherapeutic dose (28mg) did not affect the QT interval in healthy subjects.
In this trial, the primary analysis was based on the Fridericia correction factor as this correction factor is more accurate than Bazett's correction in subjects with altered heart rate as is seen following the treatment with anti-muscarinic drugs. In addition, each subject had their drug free QT/RR relationship transformed into a correction factor and integrated into an individualized QT correction formula (QTcI) that was used in supporting analysis. Results obtained using the 2 different correction factors were comparable.

Overall, the time-matched results and time-averaged results showed that treatment with 4mg/day or 28mg/day fesoterodine or with placebo resulted in a slight decrease of QTcF and QTcI with no significant difference between the active treatment groups and placebo. Mean time-averaged QTcF decreased by 4.7, 4.6, and 5.0ms after 3 days of treatment with placebo, 4mg fesoterodine, and 28mg fesoterodine, respectively. In addition, there were no statistically significant differences in the maximum change from baseline in QTcF between the active treatment groups and placebo. Outlier analyses also revealed no difference between the fesoterodine treatment groups and placebo. Assay sensitivity was shown by an increase in QTcF and QTcI after treatment with 400mg/day moxifloxacin (time-averaged increase in QTcF of 8.6ms on Day 3), which was statistically significant as compared with the fesoterodine treatment groups or with placebo. There was a higher incidence of QTcF and QTcI outliers after treatment with moxifloxacin.

As expected, there was an increase in heart rate following treatment with fesoterodine, which was more pronounced in the high dose group. This was accompanied by a concomitant decrease in the uncorrected QT interval. Other categorical analyses of ECG parameters showed similar trends at baseline and post-treatment, excluding any treatment-related effects.

No effect of treatment was observed on ECG morphology, with the exception of the expected effects of fesoterodine on heart rate.

> ***Reviewer's Comment:*** ***From the results discussed above (i.e., lack of QT prolongation in fesoterodine group observed with both uncorrected and corrected intervals), it is the opinion of this clinical reviewer that fesoterodine at both therapeutic (4mg) and supratherapeutic (28mg) doses, showed no QT-***

prolongation nor did it produce any cardiac conduction defects when compared to placebo and to a positive control, moxifloxacin.

Overall Summary for SP686:
The results from this thorough QT- study (SP686) confirms that fesoterodine does not result in any increase in QT/QTc prolongation as demonstrated under a "worst-case" scenario i.e. using a supratherapeutic dose of fesoterodine (28mg). All fesoterodine doses were well tolerated over a period of 3 days.

There were no SAE's reported, even at 28mg dose. The adverse events reported at highest incidence were those associated with anti-muscarinic effects; including: dry mouth, constipation, abdominal pain, rash, headache and urinary retention. These were observed mostly in the treatment group receiving fesoterodine 28mg daily. There were no reports of chest pain or any other cardiac abnormality in patients who received fesoterodine 4mg or 28mg daily.

Finally, the results of study SP686 provide definitive evidence that fesoterodine at anticipated maximum therapeutic dose in either extensive or poor CYP2D6 metabolizers of both genders did not demonstrate QT/QTc prolongation or any cardiac conduction abnormality.

Overall Conclusions for SP686:

- This study has demonstrated that fesoterodine both in therapeutic and supratherapeutic doses (4mg or 28mg) is not associated with prolongation of QT/QTc intervals and thereby has no clinically meaningful effect on cardiac conduction or ventricular repolarization.

- Moxifloxacin, a positive control as expected, prolonged the QTcF interval by 7msec (11%).

- Fesoterodine treatment did not result in any significant increase of cardiac intervals (QT, QRS, QTcF, QTcB, QTcI) at doses of 4 and 28 mg.

- Both fesoterodine and moxifloxacin treatments were generally well tolerated during this study.

Reviewer's Comment: It is the strong belief of this reviewer, that the results of study (SP 686) submitted in this submission provide definitive evidence that therapeutic and supra-therapeutic doses of fesoterodine resulted in no significant effect on cardiac repolarization (QT/QTcF) or cardiac conduction when compared to placebo and the active control i.e. moxifloxacin. Fesoterodine exposure in both poor and extensive metabolizers did not increase the risk of QT prolongation.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suresh Kaul
1/17/2007 03:59:57 PM
MEDICAL OFFICER

Mark S. Hirsch
1/17/2007 04:10:00 PM
MEDICAL OFFICER
I concur.