CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Division of Clinical Pharmacology 3** **Office of Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Hyunjin Kim, Pharm.D., M.S.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 05/28/2008	IND No.: Serial No.:	NDA No.: 22-030 Serial No.:	DATE OF DOCUMENT **5/1/2008 and 6/18/2008**	
NAME OF DRUG **Fesoterodine fumarate**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Pfizer (distributor), Schwarz Pharma (manufacturer)

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (Pre-IND)	☒ OTHER *(SPECIFY BELOW)*:
☐ PHASE IV RELATED		[complete response to AE letter]

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

This is a clinical pharmacology memo of complete response to FDA's "Approvable (AE)" action taken on NDA 22-030 (January 25, 2007).

Submission history

The sponsor submitted NDA 22-030 for fesoterodine fumarate, 4 and 8mg sustained release tablets on March 17, 2006 for the treatment of overactive bladder (OAB). This application received an approvable action pending sponsor's response to the following:

1. Pre-approval inspection of active pharmaceutical ingredient manufacturing facility, Schwarz Pharma LTd., located in Shannon, Ireland, which was not available during the review cycle.
2. Labeling revision. Reference is made to the revised labeling by FDA conveyed to the sponsor on January 24, 2007 for the basis for the future discussions. If additional information relating to the safety or effectiveness of fesoterodine becomes available, revision of the labeling may be required.

On May 1, 2008, the sponsor provided complete response to the AE letter with four modules (module 1, 2, 3 and 5)

- Module 1: revision of labeling conveyed to Schwarz biosciences on January 24, 2007.

- Module 2: common technical document summaries
- Module 3: quality, summary of the CMC information proposed to be included in the quality module of the complete response
- Module 5: five phase 1 clinical study reports and three study reports of uncontrolled clinical studies; Each study title and the conclusions by the sponsor are listed below.
    i. SP857: single-dose PK in Japanese subjects (Japan); "Randomized, double blind, placebo controlled, single site, dose escalation trial to investigate safety, tolerability and pharmacokinetics of fesoterodine after single oral administration of 4, 8, and 16mg doses in 12 young healthy male Japanese subjects"
        - Relative bioavailability of the pharmacologically active compound SPM 7605 was comparable for all dose levels in Japanese subjects. SPM 7605 and it metabolites (SPM 5509, SPM 7789, and SPM 7790) showed a similar plasma concentration-time profile with each dose level
    ii. SP877: single-dose proportionality (US); "Randomized, open-label, 2-fold crossover trial to investigate the dose-proportionality of fesoterodine administered as single dose administration of one 4mg tablet or one 8mg tablet in 24 healthy, male subjects" (Clinical trial report submitted in the previous NDA review cycle)
        - PK data show dose proportionality for the 2 dosage strengths (4mg and 8mg) investigated.
    iii. A0221004: multiple-dose (once daily for five days) PK in Japanese subjects (US); "A double blind, placebo controlled, multiple dose, randomized study to evaluate the safety and pharmacokinetics of fesoterodine sustained release tablets (SR) in Japanese healthy male subjects"
        - C_{max} and AUC_{τ} of SPM 7605, the active metabolite of fesoterodine, increased with dose after first and multiple-dose administrations and plasma concentrations reached steady state within 48 hours.
    iv. A0221015: multiple-dose (once daily for five days) PK in Korean subjects (Korea); "A double blind, placebo controlled, multiple dose, randomized study to evaluate the safety and pharmacokinetics of fesoterodine sustained release in Korean healthy male subjects"
        - Following single and multiple dose administrations of 4mg and 8mg once daily fesoterodine SR tablets to healthy Korean subjects, the PK profiles were consistent with those seen in Caucasian and Japanese subjects.
        - The systemic exposures of SPM 7605 increased approximately in the same proportion as the fesoterodine dose between 4mg and 8mg once daily.
    v. A0221044: single-dose proportionality and BE (US); "A phase 1, open label, randomized, single dose, 3 way crossover study to determine bioequivalence of two dose normalized E1 formulation doses as well as between formulations (E1 and F) of similar doses of fesoterodine SR tablets in healthy subjects"
        - Dose proportionality of SPM 7605 was established between the fesoterodine 4mg (E1) and fesoterodine 8mg (E1) SR tablets.
        - Bioequivalence was established between the fesoterodine 8mg (E1) and fesoterodine 8mg (F) SR tablets
    vi. SP669: Two-phase extension trial of SP668 to investigate the safety and tolerability of sustained release fesoterodine in subjects with overactive bladder: a double-blind phase followed by an open-label extension phase
    vii. SP738: Long-term open-label extension trial for subjects completing the phase 3 trial of fesoterodine (SP583) for the treatment of overactive bladder syndrome
    viii. SP739: Long-term open-label extension trial for subjects completing the Phase 3 trial of fesoterodine (SP584) for the treatment of overactive bladder syndrome

Background

Fesoterodine is a new chemical entity in the class of antimuscarinic agents. Fesoterodine itself is a relatively weak muscarinic receptor antagonist with no selectivity for any of the receptor subtypes. Nonclinical in vitro and in vivo

pharmacokinetic and toxicokinetic studies have shown a rapid deesterification of fesoterodine to its hydroxy metabolite, SPM 7605. SPM 7605 is also formed in vivo by metabolization of tolterodine, which is approved for the treatment of symptoms of OAB.

Review of submissions

Module 1, labeling revision contains a modification of METABOLISM in the Clinical Pharmacology section. CYP2D6 was previously proposed to be a major metabolic pathway to further metabolize the major active metabolite, SPM 7605 to SPM 5509. In this current submission, the sponsor is proposing to add CYP3A4 metabolic pathway, which is responsible for metabolizing SPM 7605 to SPM 7789, along with CYP2D6 as two major metabolic pathways responsible to metabolize SPM 7605. This proposal was made based on the observation of the similar increase (2 to 2.5 fold) of the exposure of SPM 7605 in CYP2D6 poor metabolizers and subjects with CYP3A4 inhibition by ketoconazole (SP564, SP567, SP683, SP684 – studies submitted at the time of original submission; March 2006). The relevant studies will be reviewed to address the label revision proposed by the sponsor in the NDA review.

Sponsor suggests that the results of the five phase 1 clinical studies confirm that the PK of fesoterodine is dose proportional and independent of the ethnicity of subjects and that the formulation E1 is bioequivalent to the final commercial formulation (F).

- There was a change of engraving from [redacted] to "FT" to the final formulation F product. A dissolution comparison to bridge this change in engraving was found to be acceptable by the Office of New Drug Quality Assessment (ONDQA).

Table 1. Compositions of Fesoterodine 4mg SR Tablets

Formulation	B*	D	E	F
Fesoterodine fumarate				
Xylitol				
Lactose monohydrate				
Microcrystalline cellulose				
Lactose monohydrate				
Hypromellose [redacted]				
Hypromellose [redacted]				
Glyceryl behenate				
Talc				
[redacted]				
Total				

* Only 4 mg strength is available for formulation B

b(4)

Table 2. Compositions of Fesoterodine 8mg SR Tablets

Formulation	C*	D	E	F
Fesoterodine fumarate				
Xylitol				
Lactose monohydrate				
Microcrystalline cellulose				
Lactose monohydrate				
Hypromellose [redacted]				
Hypromellose				
Glyceryl behenate				
Talc				
[redacted]				
Total				

* Only 8 mg strength is available for formulation C

b(4)

Table 3. Composition of Fesoterodine Fumarate Film Coated 4 mg SR Tablets Formulations E, E(1) and F

Formulation	E White film coated	E(1) [b] White film coated	F Light blue film coated
Fesoterodine fumarate			
Xylitol			
Lactose monohydrate (			
Hypromellose (			
Hypromellose (			
glyceryl behenate			
Talc			
Total			

b(4)

q.s.
a
b

Table 4. Composition of Fesoterodine Fumarate Film Coated 8 mg SR Tablets Formulations E, E(1) and F

Formulation	E White film coated	E(1) [b] White film coated	F Blue film coated
Fesoterodine fumarate			
Xylitol			
Lactose monohydrate			
Hypromellose			
Hypromellose			
glyceryl behenate			
Talc			

b(4)

q.s.
a
b

Table 5. Film Coat Composition for Formulations E, E(1) and F

	Formulation E White film coated	Formulation E (1) White film coated	Formulation F Light blue film coated (4mg)	Formulation F Blue film coated (8mg)
Polyvinyl alcohol				
Titanium dioxide				
Talc				
Soya lecithin				
Indigo carmine aluminum lake				
Total				

b(4)

Table 6. Summary of formulations and bridging performed*

Type	ID	Strength (mg)	BE link	Comments
IR		.5, 1, 2, 4	NA	Gelatin capsules filled with fesoterodine/xylitol granulate.
ER	A	8 mg with 2 different release profiles	NA	Used in SP562. Only for formulation development.
	B	4 mg	2x4 mg B was BE to 1x8 mg D	Used in phase 1 and 2 studies as multiples of 4 mg. BE study SP681.
	C	8 mg – two formulations with 320 and 440 mg total weigh	Each 8 mg C was BE to 2x4mg B	Only for formulation development. BE study SP685.
	D	4 and 8 mg (Used in phase 3)	1x8 mg D was BE to 2x4 mg B	Core of 4 mg B was changed to match C, 8 mg D core is same as C. In vitro dissolution of 4 mg D was similar to 4 mg B. BE study SP681.
	E	4 and 8 mg (Used in phase 3)	Similar in vitro dissolution profiles between E and D	D and E were used in primary trials. No BE study was needed due to level 1 change.
	F	4 and 8 mg (To-be-marketed)	Similar in vitro dissolution profiles between F and E. Similar dissolution profiles between F	To-be-marketed formulation. Minor level 1 change in film coat.

*From Dr. Doan Tran's Clinical Pharmacology Review of fesoterodine (DFS, 12/05/2006), Please refer to his review for more detailed information

List of clinical trials using extended release tablets and the corresponding formulations and strengths

- SP857: 4mg (E)
- SP877: 4mg (F) and 8mg (F)
- A0221004: 4mg (E1) and 8mg (E1)
- A0221015: 4mg (E1) and 8mg (E1)
- A0221044: 4mg (E1) and 8mg (E1, F)
- SP669: 4mg (B, D, E, F) and 8mg (D, E, F)
- SP738: 4mg (E, F) and 8mg (E, F)
- SP739: 4mg (E, F) and 8mg (E, F)

Referring to the Dr. Doanh Tran's Clinical Pharmacology review (Division Files System - DFS, 12-05-2006), the sponsor has developed 6 extended release formulations designated as A, B, C, D, E and F. Formulations A and C were used only for formulation development. Phase 3 trials for safety and efficacy used formulations D and E. Formulation F is the to-be-marketed formulation. Changes from D to E to F were minor and successfully bridged with similar in vitro dissolution profiles. Formulation E1 has been developed due to the anticipated need for drug blinding from placebo and/or key drug competitors in future comparative trials. Formulation E1 has a tablet core identical to formulation E and F and has a white coating slightly different in composition from that of formulation E. Formulation E1 was used in studies, A0221004, A0221015, and A0221044.

Review comments

- The appropriateness of sponsor's suggested two major metabolic pathways, CYP2D6 and CYP3A4, for SPM 7605 will be addressed.
- The appropriateness of sponsor's suggested dose proportionality and ethnicity independent pharmacokinetic profile of fesoterodine will be addressed.
- The appropriateness of sponsor's suggested bioequivalence between formulations E1 and F will be addressed.

Comments to the sponsor

Submit or provide the location of the following information, if submitted previously

- Method validation report (07020VCJ_PSU; A0229001) of studies A0221004, A0221015, and A0221044.
- Method validation reports and study specific bioanalytical reports of studies SP857 and SP877
- Clarify whether fesoterodine 4 and 8mg of formulation E1 were used in studies A0221004 and A0221015.

- Composition of formulation E1 of fesoterodine

Sponsor has submitted all the requested information from clinical pharmacology on June 18, 2008.

SIGNATURE OF REVIEWER: _____ **SIGNATURE OF TEAM LEADER:** _____	Date _____ Date _____
CC.: DCP3; TL: Kim; DD: Bashaw	**Project Manager:** _____ **Date** _____

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

/s/

Hyunjin Kim
7/2/2008 02:29:55 PM
BIOPHARMACEUTICS

Myong-Jin Kim
7/3/2008 08:40:57 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-030	Submission Date(s): 5/1/2008, 6/18/2008
Brand Name	Toviaz
Generic Name	Fesoterodine fumarate
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader (Acting)	Doanh Tran, R.Ph., Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Pfizer
Relevant IND(s)	51,232
Submission Type	Resubmission
Formulation; Strength(s)	Extended-release tablet, 4 and 8mg
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency

Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 3 finds the resubmission for NDA 22-030 for fesoterodine acceptable from a Clinical Pharmacology perspective. Please see the original NDA review prepared by Dr. Doanh Tran in DFS dated on December 5, 2006.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Fesoterodine is a new chemical entity in the class of antimuscarinic agents. Fesoterodine itself is a relatively weak muscarinic receptor antagonist with no selectivity for any of the receptor subtypes. Nonclinical *in vitro* and *in vivo* pharmacokinetic and toxicokinetic studies have shown a rapid deesterification of fesoterodine to its hydroxy metabolite, SPM 7605. SPM 7605 is also formed *in vivo* by metabolization of tolterodine, which is approved for the treatment of symptoms of Overactive Bladder (OAB).

The sponsor submitted NDA 22-030 for fesoterodine fumarate, 4 and 8mg extended release tablets on March 17, 2006 for the treatment of OAB. This application received an approvable action pending labeling revision and pre-approval inspection of active pharmaceutical ingredient manufacturing facility, Schwarz Pharma.

In this current submission, sponsor has submitted four newly conducted PK studies along with one PK study which was submitted and reviewed at the time of original NDA submission.

Fesoterodine exposures, in terms of AUC and C_{max}, observed in studies with Japanese (study SP857 and A0221004) and Korean (A0221015) were similar to that in study with Caucasian (study SP565 and SP566, submitted at the time of original submission) within 4 to 8mg range.

Labeling revision in metabolism section: The major metabolic enzymes responsible for the metabolism of SPM 7605 were reevaluated based on the studies submitted at the time of original NDA submission per sponsor's request. No additional studies regarding the metabolic pathways of fesoterodine were submitted.

The previous label reflects the involvement of CYP2D6 and CYP3A4 in the metabolism of SPM 7605 with identifying CYP2D6 as the major metabolic enzyme. However, a similar increase (approximately 2-fold) of exposure to SPM 7605 was observed in CYP2D6 poor metabolizers (PM) vs. CYP2D6 extensive metabolizers (EM) and subjects with CYP3A4 inhibition by ketoconazole vs. subjects without CYP3A4 inhibition (SP564, SP567, SP683, SP684 – studies submitted at the time of original submission; March 2006). Therefore, CYP3A4 and CYP2D6 were identified as two major metabolic enzymes responsible for the metabolism of SPM 7605.

Dose proportionality of SPM 7605: Study 857 indicated that the C_{max} and AUC of SPM 7605, the active metabolite of fesoterodine, increased 10-21% more than dose proportional within 4 to 16mg range following a single oral dose in Japanese subjects. In a separate study, C_{max} and AUC of SPM 7605 increased 23-33% less than dose proportional within 4 to 8mg range and plasma concentrations reached steady state within 48 hours following administration of fesoterodine in study A0221004, a multiple dose study in Japanese. The cause of these inconsistent results is not clear.

The systemic exposure of SPM 7605 in terms of C_{max} and AUC increased 17-23% more than dose proportional within 4 to 8mg range in study A0221015, a multiple dose study in Korean.

Study A0221044, in which the majority of the subjects were Caucasian with some blacks, showed the dose proportionality of fesoterodine within 4 to 8mg range.

Bioequivalence between formulation E1 and F: Formulation E was used in phase 3 trials for safety and efficacy and formulation F is the to-be-marketed formulation. Changes from formulation E to F was successfully bridged with similar *in vitro* dissolution profiles in the original NDA review. The sponsor explained that they have developed formulation E1 due to the anticipated need for drug blinding from placebo and/or key drug competitors in future comparative trials. Formulation E1 was employed in study A0221004, A0221015, and A0221044. Formulation E1 has a tablet core identical to E and F with different composition of white coating from E and F. The 8mg formulation E1 was found to be bioequivalent to 8mg formulation F under fasting condition based on the 90% CI for the ratio of AUC and C_{max} of 8mg E1 and 8mg F within the acceptable range (80-125%, study A0221044 – submitted in the current submission).

2 Question Based Review

2.1 General Attributes

2.1.1 What is the regulatory history of this NDA?

Fesoterodine is a new chemical entity in the class of antimuscarinic agents for the treatment of overactive bladder (OAB). The sponsor submitted NDA 22-030 for fesoterodine fumarate, 4 and 8mg extended release tablet on March 17, 2006 for the treatment of OAB. This application received an approvable action pending labeling revision and pre-approval inspection of active pharmaceutical ingredient manufacturing facility, Schwarz Pharma.

2.1.2 How is this review organized?

This NDA review contains the review of studies which have been submitted in the current submission and the sponsor's new labeling proposal regarding the metabolism of SPM 7605 since original NDA submission on March 2006.

Please see the original NDA review prepared by Dr. Doanh Tran in DFS dated on December 5, 2006 for detailed review of data submitted in the original NDA.

2.2. General Clinical Pharmacology

2.2.1 Is sponsor's proposal to include CYP3A4 in addition to CYP2D6 as the major metabolic enzymes responsible for the metabolism of SPM 7605 acceptable?

The effects of CYP3A4 inhibition and CYP2D6 metabolism were examined in the study SP 684, where 18 healthy male subjects were given ketoconazole twice daily for 6 days with a single dose of 8mg fesoterodine given on the fifth day.

The sponsor's proposal is acceptable based on the similar increase (approximately 2-fold) of exposure to SPM 7605 was observed in CYP2D6 poor metabolizers (PM) vs. CYP2D6 extensive metabolizers (EM) and subjects with CYP3A4 inhibition by ketoconazole vs. subjects without CYP3A4 inhibition (studies SP564, SP567, SP683, SP684 – submitted at the time of original submission; March 2006). This indicated that both CYP2D6 and CYP3A4 play equally important role in the metabolism of SPM 7605.

CYP2D6 PM have values for AUC and C_{max} that are about 2-fold higher than CYP2D6 EM. A summary of effects of CYP2D6 PM, presented as PM/EM ratios for AUC and C_{max}, are listed in table 1.

Table 1. Effects of CYP2D6 PM presented as PM/EM ratios for AUC and C_{max}

Study #	N for PM	N for EM	AUC PM/EM ratio	C_{max} PM/EM ratio
SP 564	6	12	2.23	2.23
SP 565[a]	8	16	1.96	1.73
SP 683[b]	4	8	1.41	1.31
SP 684	6	11	2.31	2.13

[a] SP 565 is the primary PK study.
[b] The small increase in SP 683 may be due to its small sample size as the result is inconsistent with the 3 other studies.

The pharmacokinetic (PK) data indicated an increase of exposure to SPM 7605 during co-administration of ketoconazole caused by CYP3A4 inhibition (figure 1 and table 2). Plasma concentrations were increased when ketoconazole was co-administered with fesoterodine in both subgroups of poor and extensive metabolizers. Exposure to SPM 7605 expressed as $AUC_{0\text{-}tz}$ and C_{max} was approximately twice as high after the combined treatment of fesoterodine and ketoconazole compared to the treatment with fesoterodine alone. This result was observed in both poor and extensive metabolizers.

In conclusion, the major metabolic enzymes responsible for the metabolism of SPM 7605 are CYP3A4 as well as CYP2D6.

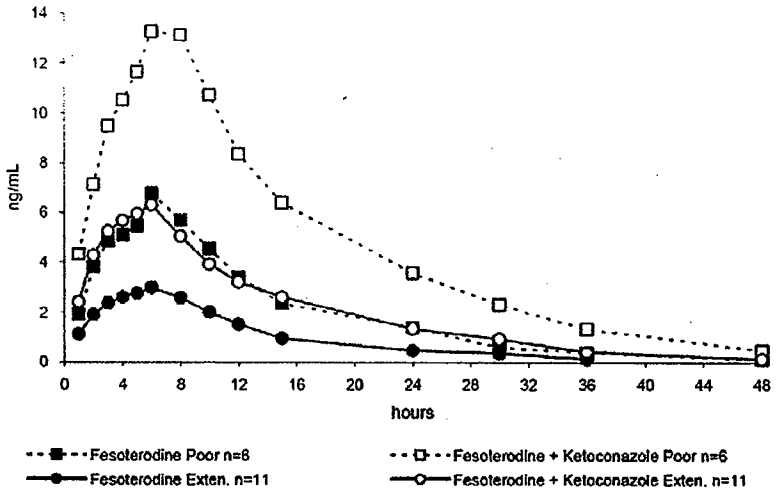

Figure 1. Plasma concentrations of SPM 7605 (arithmetic mean, study SP684) in CYP 2D6 EM and PM in the present or absent of ketoconazole 200mg twice daily*
*Original NDA review by Doanh Tran (DFS - December 5, 2006)

Table 2. PK parameter of SPM 7605 (geometric mean) in CYP 2D6 EM and PM in the present or absent of ketoconazole 200mg twice daily (study SP684)*
*Original NDA review by Doanh Tran (DFS - December 5, 2006)

Parameter	Extensive metabolizers (n=11)		Poor metabolizers (n=6)	
	feso	feso + keto	feso	feso + keto
$AUC_{(0\text{-}tz)}$ (ng/mL*h)	38.18 (39.3%)	88.28 (40.1%)	88.27 (35.3%)	217.16 (31.9%)
C_{max} (ng/mL)	2.98 (50.2%)	6.01 (44.4%)	6.36 (51.1%)	13.36 (27.9%)
$AUC_{(0\text{-}\infty)}$ (ng/mL)	39.01 (38.5%)	89.95 (39.6%)	89.50 (35.6%)	224.16 (32.7%)
Ae_{ur} (µg)	568.00 (25.1%)	760.51 (36.9%)	1263.18 (36.2%)	1373.63 (32.3%)
CL/f (L/h)	205.09 (38.5%)	88.94 (39.6%)	89.39 (35.6%)	35.69 (32.7%)
CL_R (L/h)	14.78 (23.9%)	8.60 (29.5%)	14.29 (38.1%)	6.33 (42.0%)
MRT (h)	12.60 (11.9%)	13.72 (15.2%)	13.06 (15.7%)	15.41 (20.2%)
$t_{1/2}$ (h)	6.95 (17.4%)	7.68 (21.2%)	6.98 (22.3%)	8.42 (31.9%)
t_{max} (h)*	6.0 (3.0–8.0)	5.0 (3.0–8.0)	6.0 (4.0–6.0)	6.0 (6.0–8.0)

* median (range)

2.2.2 Does fesoterodine exhibit dose proportionality in Japanese?

Study SP857 indicated that the doubling the dose resulted in approximately 10-21% more than 2-fold increase of the mean C_{max} and AUC_{0-tz} within 4 (1x4mg) to 16mg (4x4mg) range in Japanese males following administration of a single dose of formulation E (table 4). The confidence interval (CI) of the ratio of the dose normalized mean C_{max} and AUC_{0-tz} failed to meet the 80 to 125% range (table 3). In a separate study, the mean C_{max} and AUC_{τ} of SPM 7605 increased 23-33% less than proportional to dose within 4 (1x4mg) to 8mg (1x8mg) range on days 1 and 5 in Japanese males in multiple dose study A0221004 employing formulation F (table 5 and 6).

The different trend of PK in regard to dose proportionality may be explained by several factors. The samples sizes (n=12 in SP857, n=20 in A0221004) of two studies are relatively small with high variations of C_{max} and AUC reflected by 27-47% of coefficient of variations (CV). There were differences of formulations in two studies, although they were successfully bridged and reviewed in the original NDA cycle. In addition, there were demographic differences, although the inclusion criteria were similar for both studies. The mean body weight and Body Mass Index (BMI) of subjects who were enrolled in study SP857 were 58.0kg (50.0-67.0) and 19.9kg/m^2 (18.0-22.1). Those for study A0221004 were 68.5kg (54.0-92.0) and 22.9kg/m^2 (18.8-29.2). It is not clear which factors mentioned above have caused the different PK profile of two studies in regard to the dose proportionality.

Therefore, this reviewer finds that the dose proportionality of fesoterodine in Japanese inconclusive based on different trends of dose proportionality shown in study SP857 and A0221004.

Table 3. Statistical analysis of dose normalized AUC and C_{max} (study SP857)

Parameter	Treatment	LS-Mean	Ratio	Estimate	90% confidence interval
$AUC_{(0-tz)\ norm}$	4mg	341.548	4mg/8mg	0.8795	0.6635, 1.1657
	8mg	388.358	16mg/8mg	1.0658	0.8041, 1.4126
	16mg	413.903	16mg/4mg	1.2118	0.9143, 1.6062
$C_{max,norm}$	4mg	34.398	4mg/8mg	0.8621	0.6444, 1.1534
	8mg	39.902	16mg/8mg	1.0143	0.7581, 1.3570
	16mg	40.472	16mg/4mg	1.1766	0.8794, 1.5741

Table 4. Pharmacokinetic parameters of SPM 7605 following a single dose of fesoterodine in Japanese males (study SP857)

Parameter (unit)	4mg	8mg	16mg
$AUC_{(0\text{-}tz)}$ (ng/mL*h)	24.461 (38.3%)	53.715 (28.3%)	111.091 (24.3%)
$AUC_{(0\text{-}tz)\ norm}$ (ng/mL*h*kg/mg)	341.55 (37.8%)	388.36 (31.7%)	413.90 (31.1%)
C_{max} (ng/mL)	2.464 (46.5%)	5.519 (23.5%)	10.863 (22.6%)
$C_{max,\ norm}$ (ng/mL*kg/mg)	34.398 (45.4%)	39.902 (26.9%)	40.472 (30.0%)
$t_{1/2}$ (h)	9.671 (19.5%)	9.370 (22.3%)	7.558 (13.9%)
MRT (h)	13.622 (18.5%)	12.921 (11.1%)	12.449 (10.0%)
$AUC_{(0\text{-}\infty)}$ (ng/mL*h)	25.621 (36.5%)	55.587 (28.7%)	113.097 (25.0%)
$AUC_{(0\text{-}\infty)\ norm}$ (ng/mL*h*kg/mg)	357.74 (36.0%)	401.90 (32.0%)	421.38 (31.7%)
CL/f (L/h)	156.1 (36.5%)	143.9 (28.7%)	141.4 (25.0%)
CL_{ren} (L/h)	13.973 (19.0%)	12.100 (12.6%)	12.887 (26.9%)
V_z/f (L)	2178.3 (41.1%)	1945.5 (29.3%)	1542.5 (25.2%)
t_{max} (h)	5.00 (4.0-5.0)	5.00 (5.0-6.0)	5.00 (5.0-6.0)
Ae (µg)	375.47 (±132.35)	685.37 (±144.49)	1505.65 (±410.38)

Results for t_{max} show median (range)
Results for Ae show arithmetic mean (±SD)
All other parameters show geometric mean (CV)
n=8 subjects per treatment

Table 5. Summary of Pharmacokinetics by Treatment Group (Day 1, study A0221004)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=8)
AUC_τ (ng·h/mL)	n	8	8
	Geometric mean	19.9	26.9
	Arithmetic mean	21.1	29.7
	Standard deviation	8.95	11.9
	Coefficient of variation (%)	42	40
C_{max} (ng/mL)	n	8	8
	Geometric mean	1.96	2.89
	Arithmetic mean	2.07	3.09
	Standard deviation	0.856	1.14
	Coefficient of variation (%)	41	37
T_{max} (h)	n	8	8
	Median	5.0	5.0
	Minimum	2.0	2.0
	Maximum	6.0	6.0
$t_{1/2}$ (h)	n	8	8
	Arithmetic mean	8.13	6.86
	Standard deviation	3.21	1.25
	Coefficient of variation (%)	40	18

n = number of subjects, N = Number of subjects in total population, PK = pharmacokinetic

Table 6. Summary of Pharmacokinetic Parameters by Treatment Group (Day 5, study A0221004)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=8)
AUC_τ (ng·h/mL)	n	8	8
	Geometric mean	23.4	32.8
	Arithmetic mean	25.7	35.1
	Standard deviation	11.9	13.1
	Coefficient of variation (%)	46	37
C_{max} (ng/mL)	n	8	8
	Geometric mean	2.32	3.59
	Arithmetic mean	2.55	3.77
	Standard deviation	1.19	1.25
	Coefficient of variation (%)	47	33
C_{min} (ng/mL)	n	8	8
	Geometric mean	0.254	0.379
	Arithmetic mean	0.323	0.491
	Standard deviation	0.155	0.352
	Coefficient of variation (%)	48	72
CL/F (L/h)	n	8	8
	Arithmetic mean	189	262
	Standard deviation	92.3	107
	Coefficient of variation (%)	49	41
T_{max} (h)	n	8	8
	Median	5.0	5.0
	Minimum	2.0	5.0
	Maximum	5.0	5.0
$t_{1/2}$ (h)	n	8	8
	Arithmetic mean	5.13	4.86
	Standard deviation	2.54	1.69
	Coefficient of variation (%)	49	35
MRT (h)	n	8	8
	Arithmetic mean	11.0	10.7
	Standard deviation	2.22	2.10
	Coefficient of variation (%)	20	20
R_{ac}	n	8	8
	Arithmetic mean	1.20	1.25
	Standard deviation	0.264	0.308
	Coefficient of variation (%)	22	25

MRT = mean residence time, n = number of subjects, N = number of subjects in total population, PK = pharmacokinetic, R_{ac} = observed accumulation ratio

2.2.3 Does fesoterodine exhibit dose proportionality in Korean?

The mean C_{max} and AUC_τ of SPM 7605 increased 17-23% more than proportional to dose within 4 to 8mg range on day 1 and day 5 in Korean subjects in multiple dose study A0221015. The mean total clearances on day 5 were 166±49.5 and 145±51.1L/h for 4 and 8mg fesoterodine, respectively. Therefore, fesoterodine appears to be slightly more than dose proportional in Korean. However, there are some limitations of this study including the parallel design of the study, small sample size (n=8), and high variability of C_{max} and AUC reflected by 31-39% CV.

The sponsor has concluded that the pharmacokinetics of fesoterodine are dose proportional and independent of the ethnicity of subjects in regard to Japanese and Korean. However, this reviewer finds that there are differences in pharmacokinetics of fesoterodine in regard to the dose proportionality as described in section 2.2.2 and 2.2.3.

b(4)

[redacted] dose proportionality of Japanese and Korean [redacted] considering variability of data to draw the conclusion of dose proportionality and the unavailability of a study directly comparing the AUC and C_{max} of fesoterodine in Caucasian, Japanese, and Korean.

Table 7. Summary of Pharmacokinetic Parameters, by Treatment Group (Day 1, study A0221015)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=9)
AUC_τ (ng·h/mL)	n	8	9
	Geometric mean	21.5	53.1
	Arithmetic mean	22.5	56.7
	Standard deviation	7.2	21.8
	Coefficient of variation (%)	32	38
C_{max} (ng/mL)	n	8	9
	Geometric mean	2.29	5.42
	Arithmetic mean	2.40	5.84
	Standard deviation	0.75	2.30
	Coefficient of variation (%)	31	39
T_{max} (h)	n	8	9
	Median	5.0	5.0
	Minimum	3.0	3.0
	Maximum	6.0	8.0
$t_{1/2}$ (h)	n	8	9
	Arithmetic mean	7.90	7.16
	Standard deviation	2.85	1.12
	Coefficient of variation (%)	36	16

n, number of subjects. N, Number of subjects in total population. PK, pharmacokinetic.

Table 8. Summary of Pharmacokinetic Parameters, by Treatment Group (Day 5, study A0221015)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=8)
AUC_τ (ng·h/mL)	n	8	8
	Geometric mean	25.1	59.1
	Arithmetic mean	26.1	64.2
	Standard deviation	8.0	30.4
	Coefficient of variation (%)	31	47
C_{max} (ng/mL)	n	8	8
	Geometric mean	2.47	5.76
	Arithmetic mean	2.55	6.04
	Standard deviation	0.68	2.03
	Coefficient of variation (%)	27	34
C_{trough} (ng/mL)	n	8	8
	Arithmetic mean	0.35	0.91
	Standard deviation	0.18	0.53
	Coefficient of variation (%)	50	58
CL/F (L/h)	n	8	8
	Arithmetic mean	166	145
	Standard deviation	49.5	51.1
	Coefficient of variation (%)	30	35
T_{max} (h)	n	8	8
	Median	5.0	5.0
	Minimum	4.0	2.0
	Maximum	6.0	6.0
$t_{1/2}$ (h)	n	8	8
	Arithmetic mean	7.05	6.07
	Standard deviation	1.84	1.95
	Coefficient of variation (%)	26	32
MRT (h)	n	8	8
	Arithmetic mean	11.6	10.8
	Standard deviation	1.99	1.77
	Coefficient of variation (%)	17	16
R_{ac}	n	8	8
	Arithmetic mean	1.17	1.17
	Standard deviation	0.13	0.19
	Coefficient of variation (%)	11	16

MRT, mean residence time. n, number of subjects. N, number of subjects in total population. PK, pharmacokinetic. R_{ac} observed accumulation ratio.

2.2.4 What are the formulations used in the new studies in the current submission?
The following formulations were used in each study.

- SP857: 4mg (E)
- A0221004: 4mg (E1) and 8mg (E1)
- A0221015: 4mg (E1) and 8mg (E1)
- A0221044: 4mg (E1) and 8mg (E1, F)

2.2.5 Is formulation E1 bridged to formulation F?
Formulation E was used in phase 3 trials for safety and efficacy and formulation F is the to-be-marketed formulation. Changes from formulation E to F was successfully bridged with similar *in vitro* dissolution profiles in the original NDA review. The sponsor has developed formulation E1 due to the anticipated need for drug blinding from placebo and/or key drug competitors in future comparative trials. Formulation E1 has a tablet core identical to formulations E and F (table 9 and 10). However, Formulation E1 has a white coating slightly different in composition from E and F (table 11). The formulation E1 was used in the studies A0221004, A0221015, and A0221044. b(4)

Study A0221044 showed bioequivalence of 8mg E1 and 8mg F as well as dose proportionality of 4mg E1 and 8mg E1. The 90% CI for the ratio for both AUC_{inf} (CI: 95.4; 105.34%) and C_{max} (CI: 98.59, 109.89%) of SPM 7605 after the administration of 8mg E1 and 8mg F fell within the acceptance range for bioequivalence (80%, 125%), thus the 8 mg formulations of E1 and F can be considered bioequivalent (table 13). In addition, the 90% CI for the ratio for both dose normalized AUC_{inf} (CI: 89.95, 99.22%) and C_{max} (CI: 88.37, 98.51%) of SPM 7605 after the administration of 4mg E1 and 8mg E1 fell within the acceptance range for bioequivalence (80%, 125%), thus confirming dose proportionality of active metabolite SPM 7605 following administration of 4 and 8 mg E1 formulation of fesoterodine ER tablets (table 14).

In conclusion, fesoterodine E1 8mg is bioequivalent to fesoterodine F 8mg and PK of fesoterodine E1 is dose proportional within 4 and 8mg range.

Table 9. Composition of Fesoterodine Fumarate Film Coated 4 mg ER Tablets Formulations E, E1, and F

Formulation	E White film coated (mg)	E(1)[b] White film coated (mg)	F Light blue film coated (mg)
Fesoterodine fumarate			
Xylitol			
Lactose monohydrate			
Hypromellose			
Hypromellose			
glyceryl behenate			
Talc			
Total			

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Table 10. Composition of Fesoterodine Fumarate Film Coated 8 mg ER Tablets Formulations E, E1, and F

Formulation	E White film coated (mg)	E(1)[b] White film coated (mg)	F Blue film coated (mg)
Fesoterodine fumarate			
Xylitol			
Lactose monohydrate			
Hypromellose			
Hypromellose			
glyceryl behenate			
Talc			
Total			

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Table 11. Film Coat Composition for Formulations E, E1 and F

	Formulation E White film coated	Formulation E (1) White film coated	Formulation F Light blue film coated (4mg)	Formulation F Blue film coated (8mg)
Polyvinyl alcohol				
Titanium dioxide				
Talc				
Soya lecithin				
Indigo carmine aluminum lake				
Total				

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Table 12. Descriptive Summary of Pharmacokinetic Parameters (study A0221044)

		Fesoterodine 4 mg (E1) N=36	Fesoterodine 8 mg (E1) N=36	Fesoterodine 8 mg (F) N=36
AUC_{inf} (ng.hr/mL)	Geometric mean	24.3	51.6	51.4
	Arithmetic mean	26.4	55.2	55.3
	SD	11.3	20.9	22.7
	% CV	43	38	41
AUC_{inf} (dn) (ng.hr/mL)	Geometric mean	6.08	6.44	NA
	Arithmetic mean	6.60	6.89	NA
	SD	2.84	2.61	NA
	% CV	43	38	41
AUC_{last} (ng.hr/mL)	Geometric mean	23.0	49.0	48.5
	Arithmetic mean	25.0	52.6	52.1
	SD	10.6	20.1	21.2
	% CV	42	38	41
AUC_{last} (dn) (ng.hr/mL)	Geometric mean	5.76	6.13	NA
	Arithmetic mean	6.24	6.57	NA
	SD	2.65	2.51	NA
	% CV	42	38	41
C_{max} (ng/mL)	Geometric mean	2.11	4.53	4.35
	Arithmetic mean	2.26	4.79	4.64
	SD	0.87	1.57	1.77
	% CV	38	33	38
C_{max} (dn) (ng/mL)	Geometric mean	0.53	0.57	NA
	Arithmetic mean	0.57	0.60	NA
	SD	0.22	0.20	NA
	% CV	38	33	38
T_{max} (hr)	Median	6.0	6.0	6.0
	Minimum	2.0	1.0	3.0
	Maximum	6.0	7.0	8.0
$t_{1/2}$ (hr)	Arithmetic mean	8.09	8.04	8.48
	SD	2.85	2.68	2.47
	% CV	35	33	29

SD= standard deviation, CV= coefficient of variation, dn = dose normalized, NA= not applicable

Table 13. Summary of Statistical Comparisons from ANOVA Formulation E1 versus Formulation F (study A0221044)

		Adjusted Geometric Means			
Parameter	Comparison	Test	Reference	Ratio (%) (Test / Reference)	90% CI
AUC_{inf} (ng.hr/mL)	fesoterodine E1 (8 mg) versus fesoterodine F (8 mg)	51.33	51.21	100.25	(95.40, 105.34)
AUC_{last} (ng.hr/mL)	fesoterodine E1 (8 mg) versus fesoterodine F (8 mg)	48.81	48.31	101.02	(96.42, 105.84)
C_{max} (ng/mL)	fesoterodine E1 (8 mg) versus fesoterodine F (8 mg)	4.50	4.32	104.09	(98.59, 109.89)

Table 14. Summary of Statistical Comparisons from ANOVA Formulation E 4 mg versus 8mg (Dose Normalized PK parameters, study A0221044)

Parameter	Comparison	Adjusted Geometric Means		Ratio (%) (Test / Reference)	90% CI
		Test	Reference		
AUC_{inf} (ng.hr/mL)	fesoterodine E1 (4 mg) versus fesoterodine E1 (8 mg)	6.06	6.42	94.42	(89.85, 99.22)
AUC_{last} (ng.hr/mL)	fesoterodine E1 (4 mg) versus fesoterodine E1 (8 mg)	5.74	6.10	94.06	(89.77, 98.55)
C_{max} (ng/mL)	fesoterodine E1 (4 mg) versus fesoterodine E1 (8 mg)	0.52	0.56	93.30	(88.37, 98.51)

2.3 Analytical section

2.3.1 Method validation reports

All the method validation reports satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001). Method validation report of the study SP877 was reviewed and found to be acceptable at the time of original NDA submission.

Table 15. Method Validation Study reports for 4 studies

Study #	Measurement	Assay method used	Validation study Report #
SP857	SPM7605, 5509, 7789, and 7790 in human plasma	HPLC-electrospray MS / MS	BA540-03
	SPM7605, 5509, 7789, and 7790 in human urine	HPLC-electrospray MS / MS	BA572-03
A0221004	SPM 7605 in human plasma	Turbo Ion Spray LC / MS / MS	07020VCJ_PSU.DOC
A0221015	SPM 7605 in human plasma	Turbo Ion Spray LC / MS / MS	07020VCJ_PSU.DOC
A0221044	SPM 7605 in human plasma	Turbo Ion Spray LC / MS / MS	07020VCJ_PSU.DOC

2.3.2 Bioanalytical methods

All assays were validated as indicated in the referenced validation reports listed above in section 2.3.1. Validation parameters were acceptable.

3 Appendices

3.1 Individual Study Summary

3.1.1 SP857

Randomized, double-blind, placebo-controlled, single-site, dose escalation trial to investigate safety, tolerability and pharmacokinetics of fesoterodine after single oral administration of 4 (1x4mg), 8 (2x4mg), and 16mg (4x4mg) doses in 12 young healthy male Japanese subjects.

12 healthy Japanese male subjects aged between 20 and 45 years with a body mass index ranging between 18 to 25kg/m^2 were included in this trial. 8 subjects received fesoterodine and 4 subjects received placebo orally. Subjects given fesoterodine or placebo received the same number of tablets for blinding. The dose was sequentially increased from 4 to 8, and then 16mg fesoterodine. Each subject received placebo only in one of the three dose steps. Therefore, each subject received three treatments out of four possible treatments (4, 8, 16mg fesoterodine, and placebo) in three treatment periods. Wash-out period between two different dose periods was at least 1 week. All subjects enrolled in the study were extensive metabolizers for cytochrome P450 2D6. Any subjects with medical history of serious diseases of internal organs were excluded from the study.

Blood samples for the determination of SPM 7605 and its metabolites were drawn at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, and 48 hours after administration of the trial medication. Urine was collected during the following collection periods relative to intake of the trial medication: 0 (predose), 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48h.

Conclusion

- The doubling the dose has caused the mean values of C_{max} and $AUC_{0\text{-}tz}$ of SPM 7605 to be 10-21% more than proportional values regarding the different dose levels in the range of 4 to 16mg.
- Mean urinary excretion of SPM 7605 up to 48 hours increased dose proportionally in 4, 8, and 16mg fesoterodine with less than 10% difference than proportional amount.
- Total clearance of SPM 7605 remained similar with approximately 11% difference after the administration of 4, 8, and 16mg fesoterodine.
- Maximal plasma levels of four metabolites (SPM 7605, 5509, 7789, and 7790) were reached 5 hours after administration of fesoterodine.
- Half life of SPM 7605 ranged from 7.558 to 9.671 hours in three doses (4, 8, and 16mg)

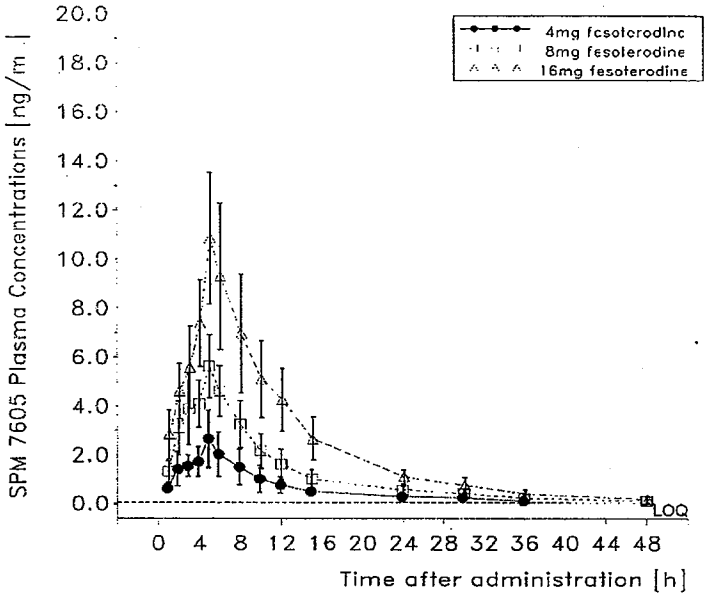

Figure 1. Plasma concentration-time profile of SPM 7605 (N=8 for each dose group, study SP857)

Table 16. Pharmacokinetic parameters of SPM 7605 (study SP857)

Parameter (unit)	4mg	8mg	16mg
$AUC_{(0\text{-}tz)}$ (ng/mL*h)	24.461 (38.3%)	53.715 (28.3%)	111.091 (24.3%)
$AUC_{(0\text{-}tz)\ norm}$ (ng/mL*h*kg/mg)	341.55 (37.8%)	388.36 (31.7%)	413.90 (31.1%)
C_{max} (ng/mL)	2.464 (46.5%)	5.519 (23.5%)	10.863 (22.6%)
$C_{max,\ norm}$ (ng/mL*kg/mg)	34.398 (45.4%)	39.902 (26.9%)	40.472 (30.0%)
$t_{1/2}$ (h)	9.671 (19.5%)	9.370 (22.3%)	7.558 (13.9%)
MRT (h)	13.622 (18.5%)	12.921 (11.1%)	12.449 (10.0%)
$AUC_{(0\text{-}\infty)}$ (ng/mL*h)	25.621 (36.5%)	55.587 (28.7%)	113.097 (25.0%)
$AUC_{(0\text{-}\infty)\ norm}$ (ng/mL*h*kg/mg)	357.74 (36.0%)	401.90 (32.0%)	421.38 (31.7%)
CL/f (L/h)	156.1 (36.5%)	143.9 (28.7%)	141.4 (25.0%)
CL_{ren} (L/h)	13.973 (19.0%)	12.100 (12.6%)	12.887 (26.9%)
V_z/f (L)	2178.3 (41.1%)	1945.5 (29.3%)	1542.5 (25.2%)
t_{max} (h)	5.00 (4.0-5.0)	5.00 (5.0-6.0)	5.00 (5.0-6.0)
Ae (µg)	375.47 (±132.35)	685.37 (±144.49)	1505.65 (±410.38)

Results for t_{max} show median (range)
Results for Ae show arithmetric mean (±SD)
All other parameters show geometric mean (CV)
n=8 subjects per treatment

3.1.2 A0221004

A double blind, placebo controlled, multiple dose, randomized study to evaluate safety and pharmacokinetics of fesoterodine extended release tablets in Japanese healthy male subjects.

This was a double-blind, placebo-controlled, multiple dose, and randomized study in healthy Japanese males. All subjects were between 18 and 50 years with BMI between 20 to 28kg/m^2. A total of 20 subjects were allocated to the 3 treatment groups as follows: 1x4 mg fesoterodine once daily (QD) (N=8), 1x8 mg fesoterodine QD (1x8mg, N=8), and placebo (N=4). Subjects received the appropriate treatment for 5 days (every morning from Days 1 to 5). Blood samples for analysis of SPM 7605 were collected up to 24 hours after dosing on Day 1. Trough concentrations prior to dosing were collected. Blood samples were also collected up to 72 hours after dosing on Day 5. All subjects enrolled in the study were extensive metabolizers for cytochrome P450 2D6. Any subjects with medical history of serious diseases of internal organs were excluded from the study.

The mean C_{max} and AUC_{τ} of SPM 7605 increased less than proportional to dose (33% and 26% less than proportional on day 1; 30% and 23% less than proportional on day 5). Total clearance after the administration of 8mg fesoterodine increased 39% compared to that after the administration of 4mg fesoterodine. The mean $t_{1/2}$ was approximately 5 hours and the C_{max} occurred 5 hours after administration of fesoterodine, regardless of doses. Overall, the mean C_{max} and AUC_{τ} of SPM 7605 increased less than proportionally.

The mean $t_{1/2}$ on Day 5 was smaller than mean $t_{1/2}$ on Day 1. Accumulation of 22% and 25% in AUC were observed following 4 and 8mg doses of fesoterodine ER, respectively after 5 days. Regardless of dose, maximum plasma levels were reached approximately 5 hours after the day 1 and 5 administration. In both the 4 and 8mg fesoterodine QD groups, C_{trough} concentrations during multiple dose administration were achieved steady state within 48 hours after the first administration (figure 3).

Table 17. Summary of Pharmacokinetics by Treatment Group (Day 1, study A0221004)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=8)
AUC_τ (ng·h/mL)	n	8	8
	Geometric mean	19.9	26.9
	Arithmetic mean	21.1	29.7
	Standard deviation	8.95	11.9
	Coefficient of variation (%)	42	40
C_{max} (ng/mL)	n	8	8
	Geometric mean	1.96	2.89
	Arithmetic mean	2.07	3.09
	Standard deviation	0.856	1.14
	Coefficient of variation (%)	41	37
T_{max} (h)	n	8	8
	Median	5.0	5.0
	Minimum	2.0	2.0
	Maximum	6.0	6.0
$t_{1/2}$ (h)	n	8	8
	Arithmetic mean	8.13	6.86
	Standard deviation	3.21	1.25
	Coefficient of variation (%)	40	18

n = number of subjects, N = Number of subjects in total population, PK = pharmacokinetic

Table 18. Summary of Pharmacokinetic Parameters by Treatment Group (Day 5, study A0221004)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=8)
AUC_τ (ng·h/mL)	n	8	8
	Geometric mean	23.4	32.8
	Arithmetic mean	25.7	35.1
	Standard deviation	11.9	13.1
	Coefficient of variation (%)	46	37
C_{max} (ng/mL)	n	8	8
	Geometric mean	2.32	3.59
	Arithmetic mean	2.55	3.77
	Standard deviation	1.19	1.25
	Coefficient of variation (%)	47	33
C_{min} (ng/mL)	n	8	8
	Geometric mean	0.254	0.379
	Arithmetic mean	0.323	0.491
	Standard deviation	0.155	0.352
	Coefficient of variation (%)	48	72
CL/F (L/h)	n	8	8
	Arithmetic mean	189	262
	Standard deviation	92.3	107
	Coefficient of variation (%)	49	41
T_{max} (h)	n	8	8
	Median	5.0	5.0
	Minimum	2.0	5.0
	Maximum	5.0	5.0
$t_{1/2}$ (h)	n	8	8
	Arithmetic mean	5.13	4.86
	Standard deviation	2.54	1.69
	Coefficient of variation (%)	49	35
MRT (h)	n	8	8
	Arithmetic mean	11.0	10.7
	Standard deviation	2.22	2.10
	Coefficient of variation (%)	20	20
R_{ac}	n	8	8
	Arithmetic mean	1.20	1.25
	Standard deviation	0.264	0.308
	Coefficient of variation (%)	22	25

MRT = mean residence time, n = number of subjects, N = number of subjects in total population, PK = pharmacokinetic, R_{ac} = observed accumulation ratio

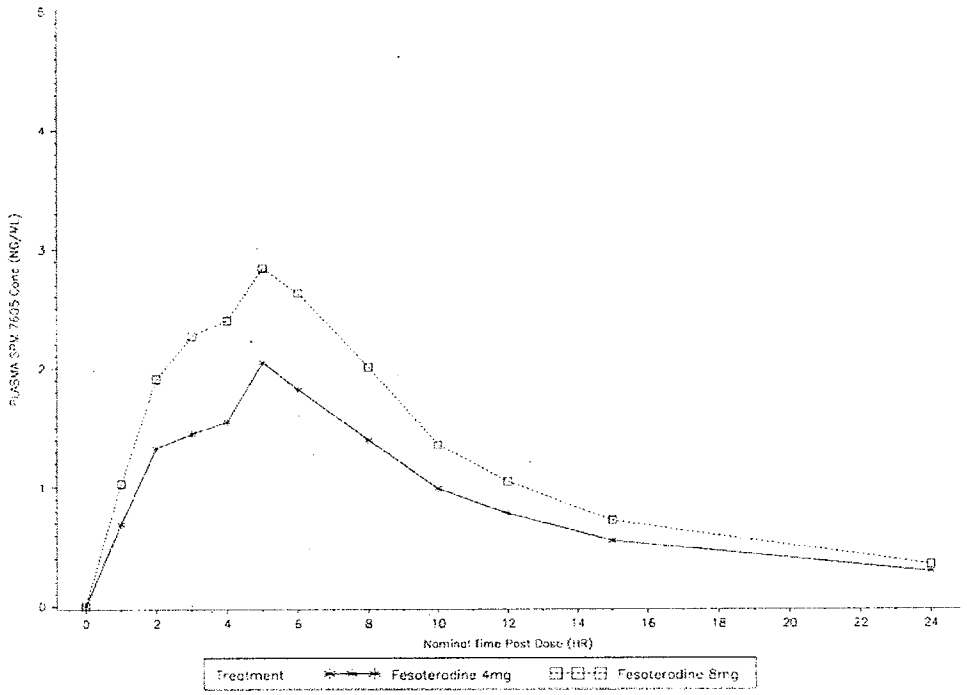

Figure 2. Mean Plasma SPM7605 Concentrations after the First Dose on Day 1 of 4mg and 8mg Fesoterodine ER Tablet QD (n=8, study A0221004)

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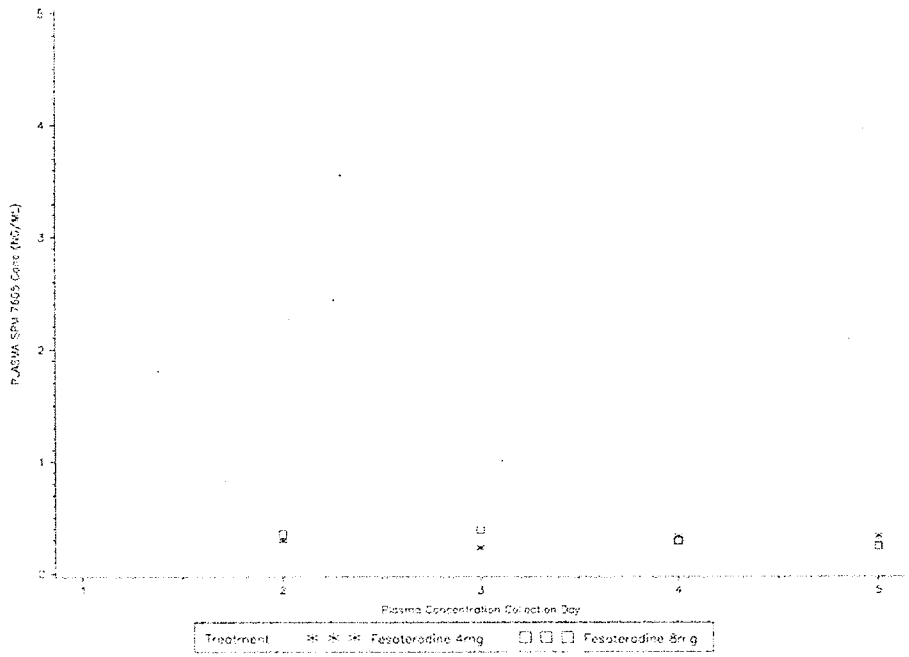

Figure 3. Mean Plasma SPM7605 Concentrations at Predose on Days 2 to 5 of 4mg and 8mg Fesoterodine ER Tablet QD (n=8, study A0221004)

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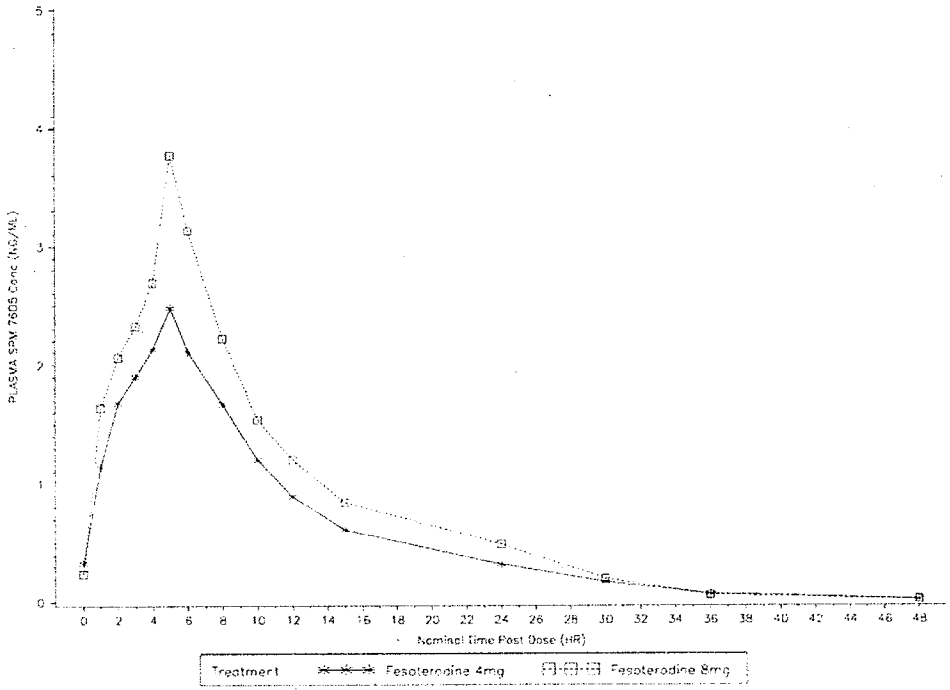

Figure 4. Mean Plasma SPM 7605 Concentrations after Last dose on Day 5 of 4mg and 8mg Fesoterodine ER Tablet QD (n=8, study A0221004)

3.1.3 A0221015

A double blind, placebo controlled, multiple dose, randomized study to evaluate the safety and pharmacokinetics of fesoterodine extended release tablets in Korean healthy male subjects

This was a double-blind, placebo-controlled, multiple dose, randomized study to evaluate the safety and PK of fesoterodine ER in healthy Korean males. A total of 20 subjects were allocated to the 3 treatment groups as follows: 4 mg fesoterodine once daily (QD) (n=8), 8 mg fesoterodine QD (n=8), and placebo (n=4). Subjects received the appropriate treatment for 5 days (every morning from Day 1 to 5). Blood samples (6 mL) to provide a minimum of 2.5 mL of plasma for PK analysis were collected into appropriately labeled tubes containing heparin, at pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15 and 24 hours after first administration at Day 1. Trough concentration before dose from Day 3 to 4 was collected. Also samples were collected at pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48 and 72 hours after last administration on Day 5. All subjects enrolled in the study were extensive metabolizers for cytochrome P450 2D6. Any subjects with medical history of serious diseases of internal organs were excluded from the study.

Regardless of dose, maximum plasma levels were reached approximately 5 hours after the day 1 and 5 administration. In both the 4 and 8mg fesoterodine QD groups, C_{trough} concentrations during multiple dose administration were achieved steady state within 48 hours after the first administration. The mean values of AUC_{τ} and C_{max} of SPM 7605

increased approximately 20% more than two times when the dose increased from 4 to 8mg on both day 1 and day 5.

Table 19. Summary of Pharmacokinetic Parameters, by Treatment Group (Day 1, study A0221015)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=9)
AUC_τ (ng·h/mL)	n	8	9
	Geometric mean	21.5	53.1
	Arithmetic mean	22.5	56.7
	Standard deviation	7.2	21.8
	Coefficient of variation (%)	32	38
C_{max} (ng/mL)	n	8	9
	Geometric mean	2.29	5.42
	Arithmetic mean	2.40	5.84
	Standard deviation	0.75	2.30
	Coefficient of variation (%)	31	39
T_{max} (h)	n	8	9
	Median	5.0	5.0
	Minimum	3.0	3.0
	Maximum	6.0	8.0
$t_{1/2}$ (h)	n	8	9
	Arithmetic mean	7.90	7.16
	Standard deviation	2.85	1.12
	Coefficient of variation (%)	36	16

n, number of subjects. N, Number of subjects in total population. PK, pharmacokinetic.

Table 20. Summary of Pharmacokinetic Parameters, by Treatment Group (Day 5, study A0221015)

PK Parameters	Summary Statistics	Fesoterodine 4 mg (N=8)	Fesoterodine 8 mg (N=8)
AUC_τ (ng·h/mL)	n	8	8
	Geometric mean	25.1	59.1
	Arithmetic mean	26.1	64.2
	Standard deviation	8.0	30.4
	Coefficient of variation (%)	31	47
C_{max} (ng/mL)	n	8	8
	Geometric mean	2.47	5.76
	Arithmetic mean	2.55	6.04
	Standard deviation	0.68	2.03
	Coefficient of variation (%)	27	34
C_{trough} (ng/mL)	n	8	8
	Arithmetic mean	0.35	0.91
	Standard deviation	0.18	0.53
	Coefficient of variation (%)	50	58
CL/F (L/h)	n	8	8
	Arithmetic mean	166	145
	Standard deviation	49.5	51.1
	Coefficient of variation (%)	30	35
T_{max} (h)	n	8	8
	Median	5.0	5.0
	Minimum	4.0	2.0
	Maximum	6.0	6.0
$t_{1/2}$ (h)	n	8	8
	Arithmetic mean	7.05	6.07
	Standard deviation	1.84	1.95
	Coefficient of variation (%)	26	32
MRT (h)	n	8	8
	Arithmetic mean	11.6	10.8
	Standard deviation	1.99	1.77
	Coefficient of variation (%)	17	16
R_{ac}	n	8	8
	Arithmetic mean	1.17	1.17
	Standard deviation	0.13	0.19
	Coefficient of variation (%)	11	16

MRT, mean residence time. n, number of subjects. N, number of subjects in total population. PK, pharmacokinetic. R_{ac} observed accumulation ratio.

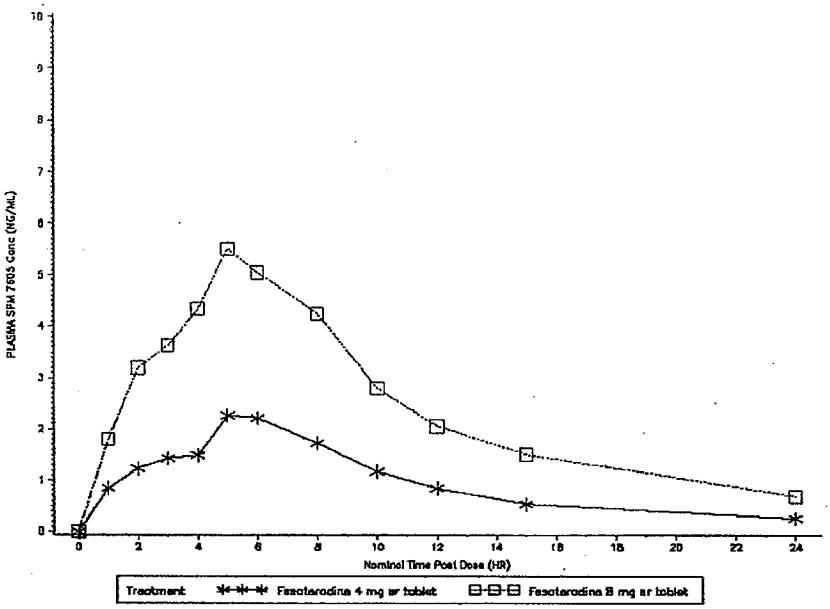

Figure 5. Mean Plasma SPM7605 Concentration-Time Profiles (Linear) - Day 1 (study A0221015)

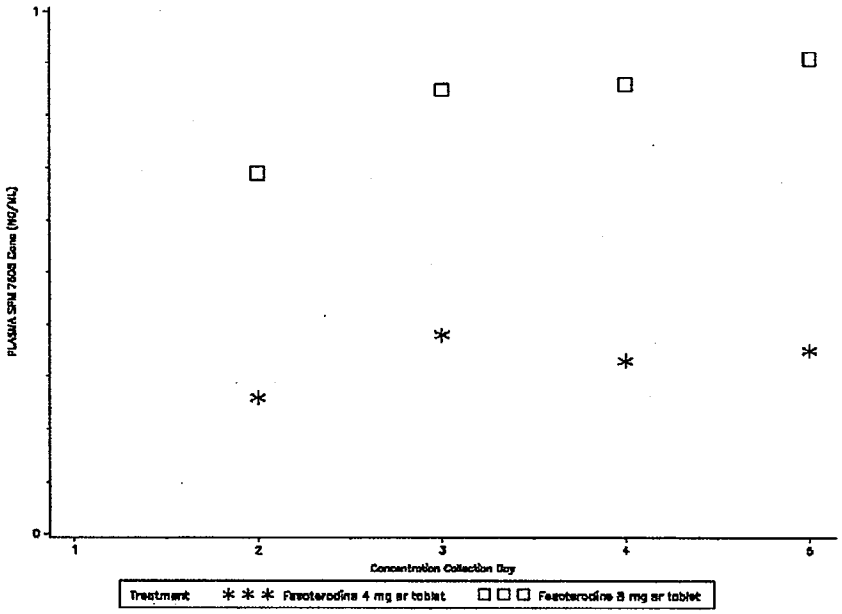

Figure 6. Mean Plasma SPM 7605 Concentration-Time Profiles (Linear) - Day 2-5 Pre-dose Concentration (study A0221015)

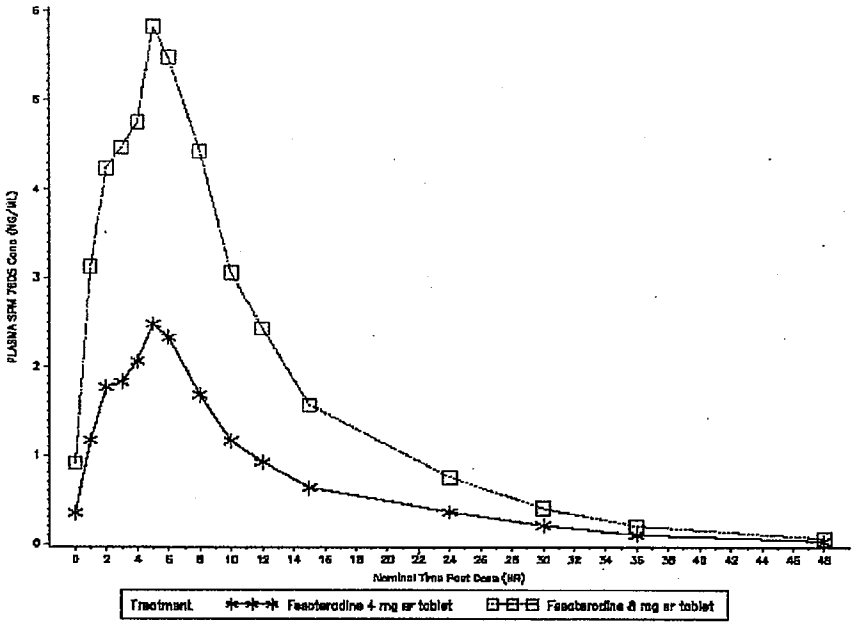

Figure 7. Mean Plasma SPM7605 Concentration-Time Profiles (Linear) - Day 5 (study A0221015)

3.1.4 A0221044

A phase 1, open label, randomized, single dose, 3-way crossover study to determine bioequivalence of two E1 formulation doses as well as between formulations (E1 and F) of similar doses of fesoterodine ER tablets in healthy subjects.

36 subjects were randomized to 3 treatment groups. On day 1 of each period between 7 and 10am, subjects received a single oral dose of the following: 4mg E1 (treatment A), 8mg E1 (treatment B), or 8mg F (treatment C). Subjects were required to fast for 10 hours prior to the serial PK blood sampling which was obtained on Day 1. Subjects remained fasted for 4 hours following the dose. Blood sample were drawn at predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, and 36 hours postdose. There was at least a 3-day washout interval between each treatment period. All subjects enrolled in the study were extensive metabolizers for cytochrome P450 2D6. Any subjects with medical history of serious diseases of internal organs were excluded from the study.

The 90% CI for the ratio for both dose normalized AUC_{inf} (CI: 89.95, 99.22%) and C_{max} (CI: 88.37, 98.51%) of SPM 7605 after the administration of 4mg E1 and 8mg E1 fell within the acceptance range for bioequivalence (80%, 125%), thus confirming dose proportionality of active metabolite SPM 7605 following administration of 4 and 8 mg E1 formulation of fesoterodine ER tablets. The 90% CI for the ratio for both AUC_{inf} (CI:

95.4, 105.34%) and C_{max} (CI: 98.59, 109.89%) of SPM 7605 after the administration of 8mg E1 and 8mg F fell within the acceptance range for bioequivalence (80%, 125%), thus the 8 mg formulations of E1 and F can be considered bioequivalent. Median T_{max} (6 hours) and mean $t_{1/2}$ (8.09 – 8.48 hours) were similar for 3 treatment groups (4mg E1, 8mg E1, and 8mg F)

Table 21. Descriptive Summary of Pharmacokinetic Parameters (study A0221044)

		Fesoterodine 4 mg (E1) N=36	Fesoterodine 8 mg (E1) N=36	Fesoterodine 8 mg (F) N=36
AUC_{inf} (ng.hr mL)	Geometric mean	24.3	51.6	51.4
	Arithmetic mean	26.4	55.2	55.3
	SD	11.3	20.9	22.7
	% CV	43	38	41
AUC_{inf} (dn) (ng.hr/mL)	Geometric mean	6.08	6.44	NA
	Arithmetic mean	6.60	6.89	NA
	SD	2.84	2.61	NA
	% CV	43	38	41
AUC_{last} (ng.hr/mL)	Geometric mean	23.0	49.0	48.5
	Arithmetic mean	25.0	52.6	52.1
	SD	10.6	20.1	21.2
	% CV	42	38	41
AUC_{last} (dn) (ng.hr/mL)	Geometric mean	5.76	6.13	NA
	Arithmetic mean	6.24	6.57	NA
	SD	2.65	2.51	NA
	% CV	42	38	41
C_{max} (ng/mL)	Geometric mean	2.11	4.53	4.35
	Arithmetic mean	2.26	4.79	4.64
	SD	0.87	1.57	1.77
	% CV	38	33	38
C_{max} (dn) (ng/mL)	Geometric mean	0.53	0.57	NA
	Arithmetic mean	0.57	0.60	NA
	SD	0.22	0.20	NA
	% CV	38	33	38
T_{max} (hr)	Median	6.0	6.0	6.0
	Minimum	2.0	1.0	3.0
	Maximum	6.0	7.0	8.0
$t_{1/2}$ (hr)	Arithmetic mean	8.09	8.04	8.48
	SD	2.85	2.68	2.47
	% CV	35	33	29

SD= standard deviation, CV= coefficient of variation, dn = dose normalized, NA= not applicable

Table 22. Summary of Statistical Comparisons from ANOVA Formulation E 4 mg versus 8mg (Dose Normalized PK parameters, study A0221044)

Parameter	Comparison	Adjusted Geometric Means		Ratio (%) (Test / Reference)	90% CI
		Test	Reference		
AUC_{inf} (ng.hr/mL)	fesoterodine E1 (4 mg) versus fesoterodine E1 (8 mg)	6.06	6.42	94.42	(89.85, 99.22)
AUC_{last} (ng.hr/mL)	fesoterodine E1 (4 mg) versus fesoterodine E1 (8 mg)	5.74	6.10	94.06	(89.77, 98.55)
C_{max} (ng/mL)	fesoterodine E1 (4 mg) versus fesoterodine E1 (8 mg)	0.52	0.56	93.30	(88.37, 98.51)

Table 23. Summary of Statistical Comparisons from ANOVA Formulation E1 versus Formulation F (study A0221044)

Parameter	Comparison	Adjusted Geometric Means			
		Test	Reference	Ratio (%) (Test Reference)	90% CI
AUC_{inf} (ng.hr mL)	fesoterodine E1 (8 mg) versus fesoterodine F (8 mg)	51.33	51.21	100.25	(95.40, 105.34)
AUC_{last} (ng.hr mL)	fesoterodine E1 (8 mg) versus fesoterodine F (8 mg)	48.81	48.31	101.02	(96.42, 105.84)
C_{max} (ng mL)	fesoterodine E1 (8 mg) versus fesoterodine F (8 mg)	4.50	4.32	104.09	(98.59, 109.89)

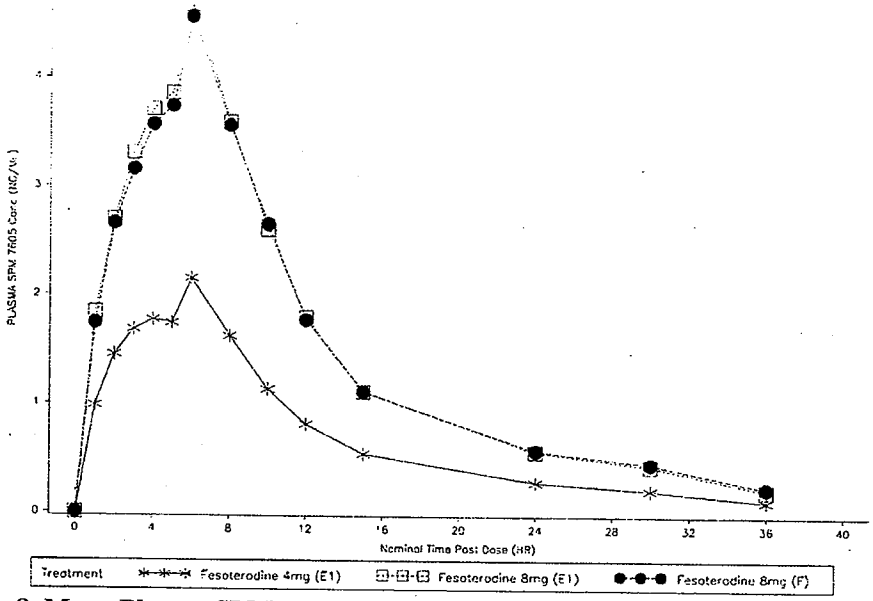

Figure 8. Mean Plasma SPM 7605 Concentration-Time Profiles Following Single Oral Administration of Fesoterodine 4mg (E1), 8mg (E1), and 8mg (F) ER Tablets (study A0221044).

3.2 Original NDA Review by Dr. Doanh Tran

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/s/

Hyunjin Kim
9/2/2008 03:44:05 PM
BIOPHARMACEUTICS

Doanh Tran
9/2/2008 04:37:45 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-030	Submission Date(s): 03/27/2006	b(4)
Brand Name	[redacted]	
Generic Name	Fesoterodine fumarate	
Reviewer	Doanh Tran, R.Ph, Ph.D	
Acting Team Leader	Myong-Jin Kim, Pharm D	
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D	
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.	
OCP Division	DCP3	
OND division	DRUP	
Sponsor	Schwarz Pharma, LLC	
Relevant IND(s)	51,232	
Submission Type; Code	Original	
Formulation; Strength(s)	Extended-release tablet, 4 and 8 mg	
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency	

Table of Contents

1 Executive Summary

1.1 Recommendation

This reviewer finds NDA 22-030 for fesoterodine fumarate acceptable from a Clinical Pharmacology perspective provided the labeling comments are adequately addressed.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Fesoterodine is a weak muscarinic receptor antagonist that rapidly de-esterifies into an active hydroxyl metabolite SPM 7605, a potent non-selective muscarinic receptor antagonist. Following oral administration, the parent compound fesoterodine can not be detected in plasma and fesoterodine's pharmacokinetics (PK) is described by its active metabolite SPM 7605. Fesoterodine is a new molecular entity but its metabolite SPM 7605 is the same as the active metabolite of the approved drug tolterodine (NDA 21228 for treatment of overactive bladder), where tolterodine and its active metabolite share total pharmacologic activity [redacted], fesoterodine is developed as an extended-release (ER) formulation. The proposed indication for fesoterodine ER is treatment of overactive bladder with symptoms of urge incontinence, urgency, and urinary frequency. b(4)

This NDA includes a comprehensive assessment of absorption, distribution, metabolism, and excretion (ADME) properties, single- and multiple-dose pharmacokinetics (both immediate and extended release), effect of sex, age, hepatic impairment, renal impairment, CYP2D6 poor metabolizer (PM), race, food, and CYP3A4 inhibition and induction on the PK of SPM 7605. Effect of fesoterodine on the PK of other drugs was evaluated in an in vivo interaction study with an oral hormone contraceptive and in vitro CYP enzyme inhibition and induction studies. Clinical safety and efficacy were evaluated in 2 phase 3 trials with supporting data from 2 phase 2 trials. The proposed doses of 4 mg/day and 8 mg/day are supported by pharmacokinetic studies and safety and efficacy trials at the same dose schedules.

Immediate release PK: Following oral administration of an immediate release (IR) formulation, fesoterodine is rapidly absorbed and hydrolyzed into SPM 7605 with T_{max} of about 1 hour. It is also rapidly eliminated with apparent terminal $t_{½}$ of about 4 hours. Steady state was reached in 3 days. [redacted] an extended release (ER) formulation approach was used in further development of fesoterodine. b(4)

Extended release PK: A single oral dose of 4 and 8 mg extended release (ER) fesoterodine resulted in mean AUC0-tz of 21.2 ± 8.1 ng*h/ml and 45.3 ± 14.5 ng*h/ml and C_{max} of 1.89 ± 0.81 and 3.98 ± 1.11 ng/ml, respectively. The ER formulation had a delayed T_{max} of about 5 hour and longer $t_{½}$ of about 7 – 8 hours. Steady state was reached in 3 days. The PK of fesoterodine was proportional in the range of 4 – 12 mg/day and potentially up to 28 mg/day. The ER formulation showed little accumulation (~17%) over 3 daily doses.

Fesoterodine is well absorbed (~85%) following oral administration of the ER formulation. Oral bioavailability of fesoterodine based on plasma concentration of SPM 7605 was 52% relative to intravenous fesoterodine.

SPM 7605 is about 50% bound to plasma protein, mainly (80%) to albumin and alpha 1 glycoprotein (AGP). SPM 7605 is distributed into tissue with apparent volume of distribution of 169L.

Fesoterodine is rapidly metabolized into SPM 7605 via nonspecific ester hydrolysis. SPM 7605 is further metabolized into SPM 5509 (mainly by CYP2D6) and SPM 7789 (mainly via CYP3A4). SPM 5509 and SPM 7789 are both further metabolized into SPM 7790. Only SPM 7605 is considered pharmacologically active based on strong binding affinity to the muscarinic receptors and relative plasma concentration.

All metabolites of fesoterodine are excreted in the urine with total urinary excretion of 70% after 96 hours. Excretion in the feces was low at 7%.

Pharmacodynamics:

The primary endpoints for treatment of overactive bladder are reduction of 1) number of micturitions and 2) number of incontinence episodes. Increase in volume voided is a secondary endpoint that is also being considered for labeling.

Fesoterodine 4 and 8 mg/day doses appear to exhibit a positive dose-efficacy response relationship for all 3 endpoints, in both phase 3 trials (SP583 and SP584). The additional benefit of 8 mg over 4 mg was modest for reduction in micturition and more substantial for incontinence episodes and volume voided. Baseline subtracted mean changes for the 3 endpoints are listed in the table below.

Endpoint	SP 583			SP 584		
	Placebo	Feso 4mg	Feso 8mg	Placebo	Feso 4mg	Feso 8mg
Micturition/24 hrs	-1.02	-1.74	-1.94	-1.02	-1.86	-1.94
Incontinence episodes/24 hrs	-1.20	-2.06	-2.27	-1.0	-1.77	-2.42
Volume voided (mL)	9.8	27.0	33.5	7.9	17.0	33.4

There was a positive dose-safety response relationship with incidence of dry mouth and constipation and increased heart rate for fesoterodine doses of 4 mg and 8 mg/day. These adverse effects may be related to the pharmacological effects of fesoterodine. The rates of other common adverse effects were low and similar to placebo.

Effect on QT: Maximum mean baseline-subtracted, placebo-corrected QTcF was 5.1 msec (upper 90% CI 9.2 msec) at 18 hour for fesoterodine 4 mg/day and 7.0 msec (upper 90% CI 11.1 msec) at 3 hour for fesoterodine 28 mg/day. However, the positive result at 28 mg dose was likely due mainly to the sharp decrease observed in the placebo group because no positive effect was observed at any other time points including the ones immediately before and after 3 hour and T_{max}. This is also supported by concentration-QTc analysis indicating a peak 95% CI upper limit QTc prolongation of 7.9 msec following 28 mg fesoterodine. In conclusion, fesoterodine 4 and 28 mg/day for 3 days did not appear to have a significant effect on QTc interval.

Effect on heart rate: Fesoterodine caused a dose dependent increase in heart rate (HR). The proportion of subjects with clinically significant heart rate increase (defined as HR increase of >25% and >100bpm) was higher in the fesoterodine treatment groups (16.9%, 39.1%, and 76.5% in the placebo, 4mg/day, and 28mg/day fesoterodine groups, respectively) likely due to the pharmacological effect of anticholinergics to increase heart rate.

Intrinsic and extrinsic factor effects on the PK of SPM 7605:

Sex, age, and race: Phase 1 studies showed the intrinsic factors sex (age group matched), age (elderly males (mean 67 yrs, range 65-69) vs. young males (mean 30 yrs, range 21 – 36)), and race (Caucasian vs. Black African) had no significant effect on the PK of fesoterodine.

Hepatic impairment: Moderate liver impairment increased SPM 7605 C_{max} and AUC by 1.4 and 2.1 fold, respectively. No dose adjustment is needed for moderate hepatic impairment due to the small increase in exposure, particularly the low 1.4-fold increase in C_{max}.

Severe hepatic impairment was not examined. This reviewer concurs with Sponsor's proposal that fesoterodine is not recommended for use in this patient population due to potentially

significant increase in exposure should severe hepatic impairment leads to reduction in both CYP2D6 and CYP3A4 activity.

Renal impairment: Values for AUC(0-tz) were 1.6-fold higher and values for Cmax were 1.3 fold higher in subjects with mild renal impairment compared to healthy subjects. In subjects with moderate renal impairment, values for AUC(0-tz) were 1.8-fold higher and values for C_{max} were 1.5 fold higher compared to healthy subjects. In subjects with severe renal impairment, values for AUC(0-tz) were 2.3-fold higher and values for C_{max} were 2.0-fold higher compared to healthy subjects.

No dose adjustment is recommended in mild and moderate renal impairment. This reviewer concurs with the sponsor's proposal of limiting patients with severe renal impairment to doses no greater than 4 mg/day.

CYP2D6 poor metabolizers: CYP2D6 poor metabolizer (PM) status was determined by genotyping or phenotyping. CYP2D6 PM alleles tested were *3, *4, *5, and *6. In some studies *2, *7, *8, and *9 were also tested. CYP2D6 PMs have values for AUC and C_{max} that are about 2-fold higher than CYP2D6 EMs. Even though the QT study indicated a positive dose response relationship with heart rate, limited data from phase 3 trial SP584 showed that in overactive bladder patients, CYP2D6 PMs did not have higher baseline corrected heart rate than EMs. Common side effects dry mouth and constipation were higher in the 8 mg group compared to 4 mg but both doses were determined to be safe in both EM and PM (see Medical Officer's review). Since the safety risk of this 2-fold increase is low, no dose adjustment is recommended in CYP2D6 poor metabolizers.

CYP2D6 inhibition: The effect of CYP2D6 inhibition was not examined but is expected to have exposure similar to CYP2D6 PM genotype. No dose adjustment is recommended for CYP2D6 inhibition.

Food: Concomitant food intake caused mean increase of AUC by 18 - 19% and C_{max} by 19 - 30% (range of two separate studies). This small increase is not clinically significant and no dose adjustment is recommended.

CYP3A4 inhibition: Inhibition of CYP3A4 by ketoconazole increased SPM 7605 AUC by 2.3 – 2.5-fold and C_{max} by 2.0 – 2.1-fold (range represents change in EM and PM, respectively). However, administration of fesoterodine to CYP2D6 PM taking ketoconazole 200 mg twice daily resulted in increases of 5.69- and 4.48-fold in AUC and C_{max}, respectively, compared to CYP2D6 EM with no concomitant CYP3A4 inhibitor. Fesoterodine 8 mg in combination with CYP3A4 inhibition and CYP2D6 inhibition/poor metabolizers may result in high drug levels (comparable to 28 mg) that could result in significant increase in heart rate and dry mouth. The 28 mg dose also caused urinary retention in some healthy volunteers. This reviewer recommends that the fesoterodine dose be restricted to no more than 4 mg/day when given to a patient taking a strong CYP3A4 inhibitor.

CYP3A4 induction: SPM 7605 AUC(0-tz) was decreased by a factor of 4.3 and 4.5 during concomitant rifampicin treatment in CYP2D6 extensive and poor metabolizers, respectively. Concomitant rifampicin treatment resulted in a decrease of C_{max} by a factor of 3.5 and 3.6 in CYP2D6 extensive and poor metabolizers, respectively. In conclusion rifampicin administration may decrease exposure to SPM 7605 and should not pose a safety concern. Therefore no dose adjustment is needed for safety, but efficacy may be reduced in the present of CYP3A4 inducers

Fesoterodine's effects on other drugs:

Oral contraceptive: Concomitant administration of fesoterodine with an oral contraceptive containing ethinylestradiol and levonorgestrel did not appear to affect the PD markers progesterone, estradiol, LH, and FSH. Fesoterodine also did not significantly affect the plasma

concentrations of ethinylestradiol and levonorgestrel as indicated by the 90% CIs that all fell within the normal limits of 80 – 125%.

General enzyme activity: Effect of fesoterodine on enzyme inhibition and induction was examined in vitro. The results indicated that fesoterodine administration is not likely to induce the activity of CYP1A2, 2B6, 2C9, 2C19, and 3A4 (i.e., all tested isoforms) or inhibit the activity of CYP1A2, 2B6, 2C9, 2C19, 3A4, or 2D6 (i.e., all tested isoforms). CYP2C8 was not evaluated.

Biopharmaceutics:

Alcohol and dose dumping: The need for direct evaluation of the effect of alcohol consumption on potential dose dumping of fesoterodine ER was considered by the entire NDA review team and determined to be not necessary following evaluation of the safety data of up to 16 mg IR and 28 mg ER doses and ' [redacted] in the formulation. b(4)

Formulations: During the development of fesoterodine, there were 6 ER formulations (designated as A, B, C, D, E, and F). Phase 3 trials for safety and efficacy used formulations D and E. Formulation F is the to-be-marketed formulation. Changes from D to E to F were minor and successfully bridged with similar in vitro dissolution profiles. Formulation F had a level 2 manufacturing change that was also successfully bridged with similar in vitro dissolution profiles in water, 0.1 N HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8. Most PK studies used formulation B, which was successfully bridged to formulation D with an in vivo bioequivalence study and dose proportionality of formulations B and F (F is equivalent to D).

Bioanalysis: Fesoterodine and its metabolites were measured in urine and plasma using validated assays and are acceptable.

An Optional OCP Inter-Divisional Level Briefing was held on 11/27/2006 with Doanh Tran, Myong-Jin Kim, Dennis Bashaw, Mark Hirsch, Suresh Kaul, Stephan Ortiz, and Sandhya Apparaju in attendance.

2 Question Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for fesoterodine?

Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

2.1.2 What are overactive bladder and its current pharmacologic treatments?

Overactive bladder (OAB) is a symptom complex defined by the International Continence Society (ICS) as the symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia. While incontinence is the worst symptom of OAB, urgency and increased urinary frequency also severely impair the quality of life of patients and reduce their well-being and social contacts. Overactive bladder affects at least 10% of the overall adult population. The majority of patients are women, who either develop OAB in combination with some degree of stress incontinence (about 30% to 40%) or as pure OAB (10% to 30%). The majority of patients with OAB have idiopathic OAB. Postulated etiologies for this condition include increased afferent activity, decreased inhibitory control, and increased sensitivity of the detrusor to efferent stimulations. 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 urinary frequency, urgency, and urge incontinence.

Current therapy for OAB focuses on managing the symptoms since the underlying cause for the condition in most cases are not known. A number of antimuscarinic agents are approved for treatment of OAB.

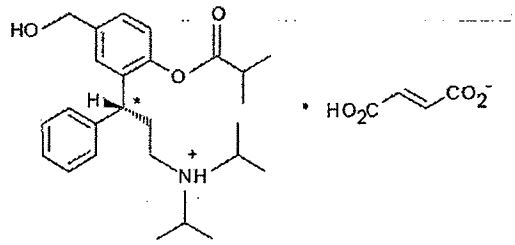
2.1.3 What is fesoterodine?

Fesoterodine (also indicated as SPM 8272) is a weak muscarinic receptor antagonist with no selectivity for any of the receptor subtypes. Upon oral administration, fesoterodine is rapidly deesterified by nonspecific esterases into its hydroxyl metabolite SPM 7605. In humans, fesoterodine can not be detected following oral administration due to the rapid hydrolysis into SPM 7605. SPM 7605 is also formed in vivo by the metabolism of tolterodine, which is an approved product for treatment of OAB. SPM 7605 is a potent non selective muscarinic receptor antagonist (Ki ranges from 1.0 – 6.3 nM to all muscarinic receptors subtypes M1 – M5) and is the main active metabolite of fesoterodine. It has at least 100-times higher affinity for the muscarinic receptor than the parent compound.

SPM 7605 further metabolizes into a major metabolite SPM 5509 (carboxy metabolite) and minor metabolite SPM 7789 (N-desisopropyl metabolite). Both SPM 5509 and SPM 7789 can be further metabolized into SPM 7790 (carboxy-N-desisopropyl metabolite). The metabolic pathway will be discussed in section 2.2.4. The binding affinity of all these metabolites was assessed in an in vitro competitive binding assay (Sponsor's report 817007). The Ki values of the main metabolite SPM 5509 for muscarinic receptors are 57- to 94-fold higher than SPM 7605. Since the exposure to SPM 5509 is only about 4-fold higher than SPM 7605, it should not significantly contribute to the pharmacologic effect of fesoterodine. The Ki values for the minor metabolite SPM 7789 were 18- to 76-fold higher than SPM7605 (based on SPM 7833 – an N-desisopropyl metabolite). SPM 7790 is a minor metabolite with exposure that is < 10% of SPM 7605 and should not contribute to the pharmacologic activity of fesoterodine because SPM 7790 did not bind to any muscarinic receptors at concentration of 1 uM (based on SPM 6923 – carboxy-N-desisopropyl metabolite) (report 817007), whereas the highest observed mean C_{max} after 8 mg fesoterodine was 21.4 nM

(7.48 ng/mL). These data suggest that SPM 7605 is the only active drug substance following fesoterodine oral administration.

Fesoterodine fumarate has a molecular weight of 527.66 and the following structure:



2.1.4 What is the pharmacologic rationale for fesoterodine in the treatment of overactive bladder?

Antimuscarinic agents exert a direct pharmacological action by antagonizing the muscarinic receptors in the bladder wall, which is thought to mediate the detrusor contraction.

2.1.5 What are the sponsor's proposed dosage and route of administration?

Fesoterodine is administered orally. The proposed recommended starting dose is 4 mg once daily. Based upon individual response, the dose may be increased to 8 mg once daily. b(4)

Fesoterodine should be taken once daily with liquid and swallowed whole. It can be administered with or without food, and should not be chewed, divided, or crushed.

For patients with severe renal impairment, the daily dose of fesoterodine should not exceed 4 mg. Fesoterodine is not recommended for use in patients with severe hepatic impairment.

2.1.6 What is the process of formulation development?

The formulation development of fesoterodine includes immediate release (IR) capsules of 0.5, 1, 2, and 4 mg. Following preliminary pharmacokinetic examination, it was determined that an extended release (ER) formulation was more suitable b(4)

The development of the ER tablet involves 6 formulations identified as A – F. Formulation B was used in phase 1 and 2 studies as multiples of 4 mg tablets. Formulations D and E were used in phase 3 safety and efficacy trials. Formulation F is the final to-be-marketed formulation. Formulations B and D were bridged with a BE study comparing 2 tablets of 4 mg B and 1 tablet of 8 mg D. The results met the BE criteria. This bridging was done to allow the use of data from phase 1 studies that used formulation B. Modification of formulations D to E and F involved minor changes that were bridged successfully with in vitro dissolution studies. b(4)
process of formulation F was also successfully bridged with dissolution studies.

The only slight uncertainty in bridging of formulation B and D is that the 4 mg D was not compared to a single 4 mg B. Indirect bridging could occur if 4 and 8 mg formulation B (as 1x4 mg or 2x4 mg) were dose proportional AND 4 and 8 mg (i.e., as 1x4 mg and 1x8 mg) of formulation D, E, or F were also dose proportional. Formulation B was dose proportional in the range of 4 – 12 mg following a single dose (SP565). The sponsor indicated in a response to 74-Day letter on 7/28/2006 that they are conducting study SP877 to investigate the dose proportionality of 1x4 mg and 1x8 mg formulation F. If SP877 shows dose proportionality between

the 4 and 8 mg tablets of formulation F, then the bridging of all formulations would be complete. A preliminary report of study SP877 showed that the 4 mg and 8 mg tablets of formulation F were dose proportional. The final study report was submitted on 11/1/2006 and confirmed this result. Therefore, bridging of all formulations used in supporting the NDA is complete.

Table 1: Summary of formulations and bridging performed

Type	ID	Strength (mg)	BE link	Comments
IR		.5, 1, 2, 4	NA	Gelatin capsules filled with fesoterodine/xylitol granulate.
ER	A	6 mg with 2 different release profiles	NA	Used in SP562. Only for formulation development.
	B	4 mg	2x4 mg B was BE to 1x8 mg D	Used in phase 1 and 2 studies as multiples of 4 mg. BE study SP681.
	C	8 mg – two formulations with 320 and 440 mg total weigh	Each 8 mg C was BE to 2x4mg B	Only for formulation development. BE study SP685.
	D	4 and 8 mg (Used in phase 3)	1x8 mg D was BE to 2x4 mg B	Core of 4 mg B was changed to match C, 8 mg D core is same as C. In vitro dissolution of 4 mg D was similar to 4 mg B. BE study SP681.
	E	4 and 8 mg (Used in phase 3)	Similar in vitro dissolution profiles between E and D	D and E were used in primary trials. No BE study was needed due to level 1 change.
	F	4 and 8 mg (To-be-marketed)	Similar in vitro dissolution profiles between F and E. Similar dissolution profiles between F [redacted]	To-be-marketed formulation. Minor level 1 change in [redacted], (a level 2 change).

b(4)

Table 1a: Composition of the to-be-marketed formulation (formulation F)

Component	Reference to standard	Function	4 mg SR tablet	8 mg SR tablet
Fesoterodine fumarate	In-house	Drug substance	4.0 mg	8.0 mg
Xylitol	USP NF			
Lactose monohydrate	DMF Holder (DMF No.			
Hypromellose	USP			
Hypromellose (	USP			
Glyceryl behenate	USP NF			
Talc	USP			
	USP			
Tablet core weight				
Total tablet weight			335.0 mg	335.0 mg

a Pharmacopoeial quality (USP)

b(4)

b(4)

Table 2: List of all clinical trials using extended release tablets and the corresponding formulation and strength.

Trial no. (phase)	Objective of trial	Dose (Formulation)
SP562 (1)	PK characterization of SR formulation	6mg (A)
SP564 (1)	PK (ketoconazole interaction)	4mg (B)
SP565 (1)	PK	
SP566 (1)	maximum tolerated dose, PK	
SP568 (1)	PK (renal impairment)	
SP569 (1)	PK (hepatic impairment)	
SP570 (1)	PK (age and gender)	
SP582 (2b)	efficacy, safety, dose finding	
SP649 (1)	PK (ethnic origin)	
SP677 (1)	hormonal contraception interaction	
SP668 (2b)	efficacy, safety	
SP669 (2b) open label	Safety	4mg (B, D, E, F) 8mg (D, E, F)
SP685 (1)	bioavailability, bioequivalence	4mg (B) 8mg (C)
SP567 (1)	absolute bioavailability, mass balance	4mg (B) 8mg (D)
SP583 (3)	efficacy, safety	4mg (D) 8mg (D, E)
SP584 (3)	efficacy, safety	
SP681 (1)	bioequivalence	4mg (B) 8mg (D)
SP683 (1)	PK (rifampicin interaction)	8mg (E)
SP684 (1)	PK (ketoconazole interaction)	8mg (D)
SP686 (1)	thorough QTc trial	4mg (E)
SP687 (1)	food effect	8mg (D)
SP738 (3) open label	safety	4mg (E, F) 8mg (E, F)
SP739 (3) open label	safety	
SP842 (1)	bioequivalence	8mg (E, F[a])

a. Manufactured by SCHWARZ PHARMA Manufacturing Inc., Seymour, Indiana, USA

PK = Pharmacokinetics

2.2 General Clinical Pharmacology

2.2.1 What is the pharmacokinetics of fesoterodine and its active metabolite SPM 7605 following oral administration?

This section is subdivided into 4 sections: 1. IR, single dose, 2. IR, multiple dose, 3. ER, single dose, 4. ER, multiple dose.

2.2.1.1 Immediate release, single-dose:

Following IR capsule oral administration (SP560), fesoterodine is rapidly absorbed and rapidly metabolized into its active metabolite, SPM 7605. SPM 7605 had a median T_{max} of 0.75 to 1 hour and an elimination half-life of about 4 hours. The exposure (AUC and C_{max}) appears dose proportional in the studied range of 0.5 to 16 mg. Food increased AUC by about 20% but had no apparent effect on C_{max}. T_{max} was delayed by food intake by about 1.5 hours. CYP2D6 status had an effect on fesoterodine PK. Comparing the 4 mg dose groups, the C_{max} and AUC were 1.6 and 2.0 fold higher, respectively, in CYP2D6 PM vs. EM. Table 3 shows the PK parameters following single dosing of IR fesoterodine capsules. Figure 1 shows the plasma concentration profile of 8 mg dose (mean ± SD).

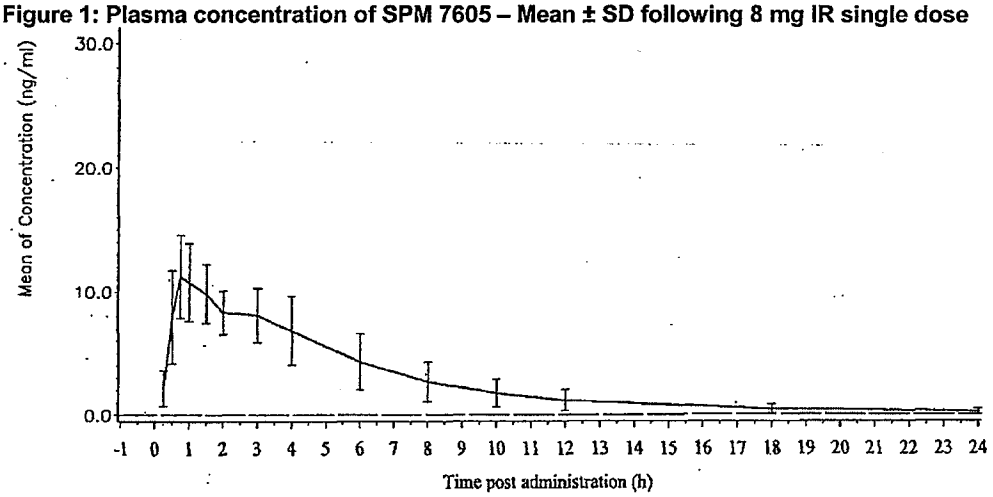
Table 3: SPM 7605 plasma PK following single dose of fesoterodine IR capsules

Mean ± SD for AUC and C_{max}, median (range) for t_{max} and $t_{1/2}$

Dose SPM8272		N	AUC_{0-t} (ng·h/ml)	C_{max} (ng/ml)	t_{max} (hh:mm)	$t_{1/2}$ (hh:mm)
A	0.5 mg	6	3.3 ± 1.6	1.0 ± 0.5	0:45 (0:30-1:30)	3:41 (1:45-3:55)
B	1 mg	6	6.5 ± 2.7	1.7 ± 0.6	1:00 (0:45-1:30)	4:24 (2:14-5:54)
C	2 mg	6	13.5 ± 2.0	2.8 ± 0.6	0:52 (0:30-1:30)	4:19 (2:46-4:44)
D	4 mg extensive metabolizer	6	23.9 ± 5.0	6.4 ± 1.6	0:45 (0:15-1:00)	3:53 (2:52-4:58)
D	4 mg poor metabolizer	6	47.9 ± 13.1	10.0 ± 2.4	0:52 (0:30-1:00)	5:05 (4:40-5:38)
E	4 mg extensive + fed	6*	28.9 ± 7.1	6.3 ± 1.8	2:00 (0:30-3:00)	4:02 (3:47-4:36)
F	8 mg	6	63.5 ± 25.9	11.9 ± 3.2	0:45 (0:45-1:30)	5:03 (3:56-5:16)
G	12 mg	6	72.1 ± 30.8	15.0 ± 5.0	0:52 (0:30-3:00)	3:36 (3:00-4:52)
H	16 mg	6	108.1 ± 35.7	23.4 ± 8.3	0:45 (0:30-1:30)	3:56 (3:32-4:55)

* Note: A total of 64 subjects were included in the trial. Subjects in group E (4 mg SPM8272, extensive metabolizer under fed conditions) were the same subjects as in group D (4 mg SPM8272 extensive metabolizer under fasted conditions).

Figure 1: Plasma concentration of SPM 7605 – Mean ± SD following 8 mg IR single dose



2.2.1.2 Immediate release, multiple-dose:

Multiple dose PK of the IR formulation was examined in study SP561. Groups of 12 healthy male subjects (9 treatment, 3 placebo) were given fesoterodine 1, 2, or 4 mg twice daily for 7 days.

The parent fesoterodine was not measurable in plasma samples. SPM 7605 appeared rapidly and reached C_{max} between 0.5 and 1 hour, consistent with results from study SP560. SPM 7605 then was cleared rapidly from plasma with a terminal half life of about 3 hours. C_{max} and amount excreted in the urine (A_e) appeared dose proportional. AUC showed a trend of over-proportional at the 4 mg level as a 4 fold increase in dose led to a mean AUC increase of 5.57 folds on Day 1 and 5.32 folds at steady state. The over-proportionality is different than observed in the single dose study and apparently due to a lower AUC for 1 mg dose (5.0 vs. 6.5 ng*h/mL) and a higher AUC for the 4 mg dose (28.5 vs. 23.9 ng*h/mL) in this study. Similar C_{trough} values (pre-morning dose) on Day 3 and Day 5 indicate that steady state was reached by Day 3. This is consistent with the short half life observed.

Steady state AUC values were 17 – 27% higher than after first dose indicating little accumulation. C_{max} values were similar between Day 1 and Day 7.

Table 4: PK values for single and multiple dose IR formulation of fesoterodine

	Dose (mg)	Day 1	Day 7	Day 7/Day 1 ratio
C_{max} (ng/ml)	1	1.715±0.924	1.883±0.997	1.10
	2	2.486±0.937	2.744±0.924	1.10
	4	6.882±3.306	6.982±3.657	1.01
AUC (ng*h/mL)[a]	1	4.968±2.052	6.285±3.144	1.27*
	2	9.536±3.659	11.164±3.862	1.17**
	4	28.450±14.947	33.415±19.658	1.17**
T_{max} (h)[b]	1	0.50 (0.50-1.50)	1.00 (0.50-1.00)	-
	2	1.00 (0.50-1.50)	1.00 (0.50-1.50)	
	4	1.00 (0.50-1.50)	1.00 (0.50-2.00)	
$T_{½}$ (h)	1	2.28±0.40	2.52±0.35	-
	2	2.47±0.33	2.78±0.35	
	4	2.72±0.42	3.01±0.70	

[a] AUCinf on day 1 and AUC0-12 on day 7; [b] median (range); * p<0.05; ** p<0.01

2.2.1.3 Extended release, single-dose:

Single dose pharmacokinetics for ER tablets of fesoterodine was determined in study SP565. 24 healthy Caucasian males (16 CYP2D6 EM and 8 PM) were given the following in random order.

A: single oral dose administration of 4 mg in a fasted state
B: single oral dose administration of 8 mg in a fasted state
C: single oral dose administration of 8 mg in a fed state
D: single oral dose administration of 12 mg in a fasted state

The results showed that T_{max} was reached in about 5 hours as a result of the ER formulation. CYP2D6 poor metabolizers had lower total body clearance and resulted in AUC and C_{max} that were about twice as high as EM subjects (table 5). $T_{½}$ were similar between PM and EM subjects (about 8 hours, table 5) and slightly lowered when taken with food.

Table 5: Geometric Means and CVs of AUC(0-tz), C_{max} and $t_{½}$ for poor (n=8) and extensive metabolizers (n=16) (SP565)

Dose SPM 8272	CYP450 2D6 Metabolizer	AUC(0-t_z) [ng*h/mL]	C_{max} [ng/mL]	$t_{1/2}$ [h]
4 mg	extensive	21.2 / 38%	1.89 / 43%	7.31 / 27%
	poor	40.5 / 31%	3.45 / 54%	7.31 / 30%
8 mg fasted	extensive	45.3 / 32%	3.98 / 28%	8.59 / 41%
	poor	88.7 / 36%	6.90 / 39%	7.66 / 21%
8 mg fed	extensive	55.4 / 29%	5.41 / 27%	5.45 / 28%
	poor	98.3 / 35%	8.62 / 29%	6.48 / 16%
12 mg	extensive	70.9 / 32.7%	6.11 / 32%	8.66 / 40%
	poor	128.7 / 40%	10.42 / 43%	9.37 / 33%

Table 6: Medians/Geometric Means and Ranges/CVs for T_{max}, HVD and CL_{tot}/f for poor (n=8) and extensive metabolizers (n=16) (SP565)

Dose SPM 8272	CYP450 2D6 Metabolizer	t_{max} [h]	HVD [h]	CL_{tot}/f [ml/min]
4 mg	extensive	5.0 (2-6)	7.8 (5-12)	1947 (37.7%)
	poor	5.0 (5-6)	9.9 (2-14)	1013 (32.3%)
8 mg fasted	extensive	5.0 (3-6)	8.4 (5-11)	1787 (31.9%)
	poor	5.0 (5-6)	9.6 (6-13)	927 (36.5%)
8 mg fed	extensive	4.5 (2-10)	7.6 (5-15)	1532 (28.9%)
	poor	5.0 (3-6)	8.3 (6-14)	855 (35.7%)
12 mg	extensive	5.0 (3-6)	7.4 (6-12)	1701 (33.0%)
	poor	5.0 (4-8)	8.0 (3-14)	950 (44.7%)

The amount of SPM 7605 excreted in the urine were almost twice as much in PM compared to EM subjects while renal clearance were similar, consistent with SPM 7605 metabolism by CYP2D6 and higher plasma SPM 7605 level in PM subjects (table 7).

Table 7: Geometric Means and CVs of Ae and CL_R for poor (n=8) and extensive metabolizers (n=16) (SP565)

Dose SPM 8272	CYP450 2D6 Metabolizer	Ae [µg]	CL_R [ml/min]
4 mg	extensive	374.37 / 32.0%	281.1 / 31.7%
	poor	608.55 / 26.9%	230.1 / 13.8 %
8 mg fasted	extensive	752.96 / 33.4%	261.8 / 27.0%
	poor	1437.2 / 33.8%	255.4 / 17.8 %
8 mg fed	extensive	910.07 / 27.2%	258.2 / 27.2%
	poor	1615.0 / 27.4%	265.1 / 12.2 %
12 mg	extensive	1137.8 / 29.3%	256.3 / 26.3%
	poor	1896.3 / 30.0%	236.1 / 23.4%

Food increased mean AUC by 18% and C_{max} by 30% (table 8, column C/B). This change is not clinically relevant. Another food effect study SP687 showed similar results. Please see section 2.4.1 for more detailed discussion of food effect on PK.

Dose normalized AUC and C_{max} were similar and suggests dose proportionality in the range of 4 – 12 mg (table 8).

Table 8: Treatment Ratios or differences (*) and 90% Confidence Intervals (SP565). See beginning of this section for definition of A, B, C, and D.

Parameter	A / B	D / B	C / B
AUC(0-t_z) geometric, dose-corr.	92.77% (87%,99%)	101.73% (95%,109%)	118.32% (110%,127%)
C_{max} geometric, dose-corr.	92.01% (82%,104%)	102.06% (92%,113%)	130.01% (123%,141%)
t_{max}* arithmetic	±0.0% (-10%,+0%)	±0.0% (-10%,+10%)	-10.0% (-20%,+0%)
HVD* arithmetic	-2.59% (-13%,+8%)	-4.97% (-15%,+5%)	-1.63% (-12%,+9%)
$t_{1/2}$ geometric	88.46% (78%,100%)	107.52% (94%,122%)	69.85% (61%,79%)
Ae* arithmetic, dose-corr.	-8.15% (-15%,-1%)	-5.01% (-12%,+2%)	+15.90% (+9%,+23%)
CL_R geometric	102.10% (95%,110%)	96.04% (89%,103%)	101.67% (94%,110%)

2.2.1.4 Extended release, multiple dose:

Multiple dose pharmacokinetics of fesoterodine was examined in study SP566. The trial was a multiple-dose, sequential, ascending dose study with the following doses 4, 8, 12, 20, and 28 mg given once daily for 3 days. A 40 mg arm was planned but not conducted since maximum tolerated dose was reached at 28 mg. There were 8 subjects in each dose level (6 on fesoterodine and 2 on placebo). Subjects were not stratified by CYP2D6 status. However, there was one PM subject in each of the 4, 8, and 12 mg dose groups that received fesoterodine. Subjects in 20 and 28 mg dose groups and all placebo subjects were EMs. Pharmacokinetics was monitored up to 24 hours after last dose.

Figure 2 shows the PK profiles for all dose levels. T_{max} were about 4 – 6 hours. C_{max} and AUC increased linearly with dose (table 9). Figures 3 and 4 show the mean concentrations following daily doses of 4 and 8 mg fesoterodine over 3 days, respectively. Modest accumulation of 13% and 17% in AUC were observed following 4 and 8 mg doses of fesoterodine ER, respectively, after 3 days. Examination of C_{max} and AUC suggests that steady state was reached by Day 3. C_{max} values were similar between Days 1, 2, and 3 and AUC_{0-24} values on Day 3 were approximately equal to that of $AUC_{0-\infty}$ estimated on Day 1.

Figure 2: Mean SPM 7605 profiles on Day 1 – 3

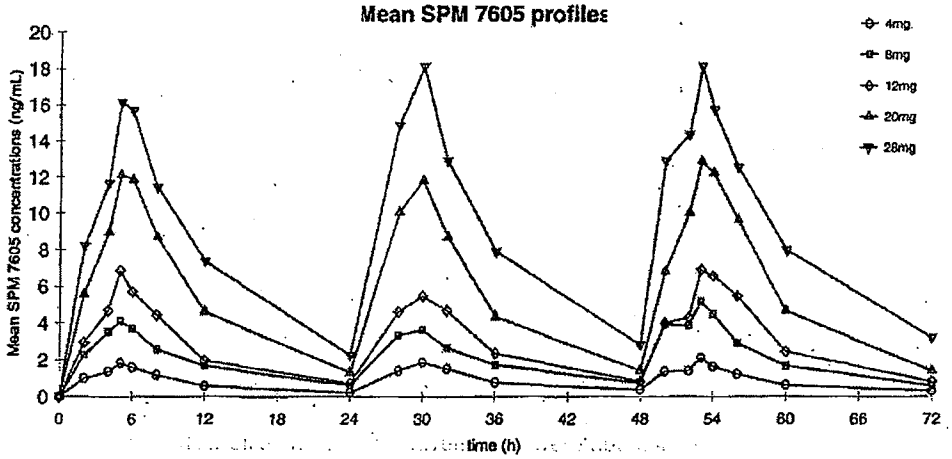


Figure 3: Mean (SE) SPM 7605 PK profile following 4 mg fesoterodine ER over 3 days

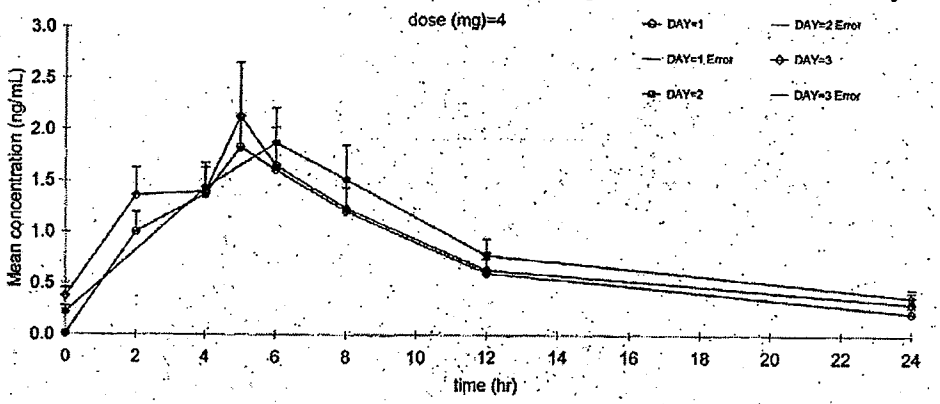


Figure 4: Mean (SE) SPM 7605 PK profile following 8 mg fesoterodine ER over 3 days

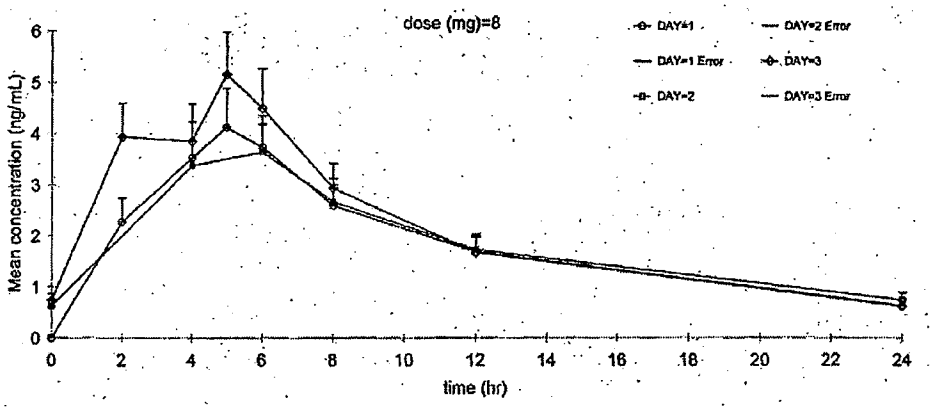


Table 9: Mean (SD) PK parameters for SPM 7605 following dosing of fesoterodine ER

Day	Parameter	4 mg Mean(SD)	8 mg Mean(SD)	12 mg Mean(SD)	20 mg Mean(SD)	28 mg Mean(SD)
1	C_{max} (ng/mL)	2.19(0.66)	4.31(1.79)	6.88(3.21)	12.36(6.07)	16.29(5.69)
	t_{max} (hr)	5.17(0.75)	4.83(0.75)	5.00(0.00)	5.50(0.55)	5.50(0.55)
	C_{trough} (ng/mL)	0.01(0.02)	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.00(0.00)
	λ_z (1/hr)	0.12(0.03)	0.10(0.02)	0.11(0.03)	0.12(0.02)	0.11(0.04)
	$t_{1/2}$ (hr)	6.11(1.15)	7.42(2.03)	6.75(2.57)	5.87(0.79)	6.94(3.13)
	AUC_{0-24} (hr*ng/mL)	17.99(7.16)	44.48(17.47)	61.81(18.43)	126(49)	181(59.74)
	AUC_{0-Inf} (hr*ng/mL))	20.09(8.60)	51.79(20.66)	69.29(18.20)	137(54.28)	208(68.96)
	A_e (mcg)	263(88.2)	662(246)	1132(479)	1678(506)	1681(640)
2	C_{max} (ng/mL)	1.92(0.84)	3.73(1.35)	5.63(1.59)	12.01(5.86)	18.14(3.57)
	t_{max} (hr)	5.67(0.82)	5.67(0.82)	5.67(0.82)	5.67(0.82)	6.00(0.00)
	C_{trough} (ng/mL)	0.22(0.14)	0.62(0.33)	0.73(0.22)	1.31(0.65)	2.26(1.46)
	AUC_{0-24} (hr*ng/mL)	21.39(9.60)	44.82(17.00)	63.97(16.11)	126(60.42)	204(50.74)
	A_e (mcg)	305(127)	708(305)	1178(515)	1744(420)	2542(646)
3	C_{max} (ng/mL)	2.12(1.28)	5.15(2.02)	7.11(3.01)	13.25(7.26)	18.28(6.31)
	t_{max} (hr)	4.17(2.04)	5.00(0.00)	5.67(1.21)	5.33(0.52)	5.17(0.41)
	C_{trough} (ng/mL)	0.37(0.19)	0.74(0.33)	0.82(0.37)	1.41(0.72)	2.81(1.61)
	λ_z (1/hr)	0.12(0.07)	0.11(0.02)	0.11(0.03)	0.12(0.03)	0.09(0.04)
	$t_{1/2}$ (hr)	7.76(4.09)	6.54(0.91)	6.37(1.55)	6.07(1.16)	8.04(2.07)
	AUC_{0-24} (hr*ng/mL)	20.26(11.44)	52.03(21.76)	72.87(25.37)	136(68.76)	213(73.28)
	CL_{tot}/f (L/min)	5.81(6.63)	3.41(2.63)	3.10(1.29)	2.89(1.10)	2.42(0.80)
	MRT (hr)	12.97(5.65)	10.79(0.87)	11.26(1.94)	10.99(1.68)	13.39(2.69)
	Vz/f (L)	2749(1447)	1839(1154)	1768(947)	1551(624)	1663(717)
	A_e (mcg)	317(184)	671(307)	1364(487)	1757(363)	2426(593)
	Cl_{ren} (L/min)	0.26(0.07)	0.21(0.04)	0.33(0.10)	0.24(0.06)	0.20(0.07)

2.2.2 What is the absolute bioavailability of fesoterodine?

Absolute bioavailability of fesoterodine as compared to intravenous (iv) administration, as 4-hour infusions, was evaluated in study SP567. In the primary PK portion of this study, 3 groups of healthy male subjects were dosed with 8 mg fesoterodine orally, 4 mg fesoterodine iv, or 2.6 mg SPM 7605 iv (equal molar to 4 mg fesoterodine).

Fesoterodine was well absorbed (~85%) based on the proportion of all metabolites excreted in urine following oral dose (69.71%) and iv dose (82.24%). Excretion in feces was low (6.84% for oral and 2.41% for iv). The slightly higher feces excretion proportion suggests that some fesoterodine was metabolized to SPM 7605 in the GI tract. The oral bioavailability of fesoterodine based on SPM 7605 plasma AUC was 52%. If all metabolites (i.e., SPM 7605, 5509, 7789, and

7790) were considered, the bioavailability was about 88% (Table 11). High amount of SPM 7789 and 7790 following oral dosing might be due to first pass metabolism.

From the same data (i.e., relative bioavailability of each metabolite and renal elimination), sponsor proposed that fesoterodine is [redacted] b(4)
This reviewer notes that bioavailability of SPM7789 and 7790 were >100%. However, these are not considered active metabolites and can be explained (as sponsor proposed) by first pass metabolism. These metabolites alone should not be used to indicate oral absorption of fesoterodine.

The $t_{1/2}$ following oral administration of ER formulation was longer than following iv dosing (7.21 vs. 4.29 hour). The terminal half life of SPM 7605 did not appear to be formation rate limited as its half life following iv dosing of itself was very similar at 4.21 hours. The data suggest the apparent half life of SPM 7605 following oral fesoterodine to be absorption rate limited. Absorption rate limited eliminations were also observed for the other metabolites.

Table 10: PK parameters of SPM 7605

Parameter	Unit	Arithmetic mean (CV%)		
		8mg fesoterodine SR tablet (n=11)	4mg fesoterodine iv (n=11)	2.6mg SPM 7605 iv (n=11)
C_{max}	ng/mL	4.69 (43.1)	8.40 (18.0)	10.62 (18.4)
$AUC_{(0-t)}$	ng/mL*h	51.7 (26.8)	49.8 (17.3)	61.1 (18.6)
$AUC_{(0-\infty)}$	ng/mL*h	52.6 (26.6)	50.6 (17.2)	61.8 (18.4)
$t_{½}$	h	7.21 (25.2)[2]	4.29 (10.0)	4.21 (17.4)
t_{max}[1]	h	5.00 [5.00–6.00]	3.98 [3.98 – 3.98]	3.98 [3.00 – 3.98]
V_{area}/fm'	L	2748 (57.4)	-	-
V_{ss}/fm	L	-	519 (24.9)	-
V_{ss}	L	-	-	169 (17.1)
Ae_{ur}	µg	839.8 (26.3)	705.8 (22.1)	879.8 (19.7)
Ae_{fe}	µg	228.5 (85.1)	1.1 (331.7)	0.0
CL_R	L/h	16.4 (11.3)	14.2 (13.8)	14.4 (8.6)

Data source: Table 49.1, Table 49.2, Table 49.3, Table 72.1, Table 72.2, Table 72.3, Table 91.1, Table 91.2. Table 91.3

[1]Median and range are given for t_{max}

[2]Apparent terminal elimination half-life; not likely to be a representation of its true elimination.

Table 11: Mean (arithmetic) $AUC_{0-\infty}$ following oral and iv dosing of fesoterodine (not corrected for molecular weight)

AUC (ng*h/mL)	8 mg fesoterodine ER	4 mg fesoterodine iv
SPM 7605	52.6	50.6
SPM 5509	208.4	123.6
SPM 7789	3.99	0.569 *(AUC_{0-t})
SPM 7790	127.7	49.2
Total of all metabolites	392.7	224.0

2.2.3 What are protein binding and distribution properties of fesoterodine?

Plasma protein binding for SPM 7605 was examined in the in vitro study report 496-02 and also measured as fraction unbound in the renal impairment study SP568. The table below shows the protein binding fraction for both the parent fesoterodine and metabolite SPM 7605 from study report 496-02. SPM 7605 had a mean binding of 53 ± 2% to plasma. Binding with albumin and alpha 1 glycoprotein (AGP) occurred with a mean of 39 ± 1% bound to a solution containing both albumin and AGP indicating a majority of plasma SPM 7605 binding was to these 2 proteins. SPM 7605 binding to these 2 components of plasma was less than the 91 ± 6% binding observed with the parent fesoterodine under similar conditions. This suggests that the low observed plasma binding of fesoterodine (i.e., 51%), which was similar to SPM 7605, was due to metabolism of SPM 8272 to SPM 7605 during the 2 hour incubation during the 2-hr equilibrium dialysis incubation. Separately, study SP568 showed that the fraction unbound in plasma was 0.54 (8.4% CV) (i.e., a binding fraction of about 46%) following administration of 4 mg fesoterodine to subjects with normal renal function. In conclusion, from the two studies, it appears that SPM 7605 plasma protein binding is about 50% with most bound to albumin and AGP.

Table 12: Protein binding (mean % ± SD)

	Human plasma	Albumin (45 mg/mL)	AGP (1 mg/mL)	Albumin + AGP
SPM 8272	51±4	30±2	72±7	91±6
SPM 7605	53±2	14±3	16±9	39±1

Tissue distribution of SPM 7605 is evident by the large steady state volume of distribution (169 L) observed following iv dosing of itself (table 10 above).

2.2.4 What is the metabolic pathway for SPM 7605?

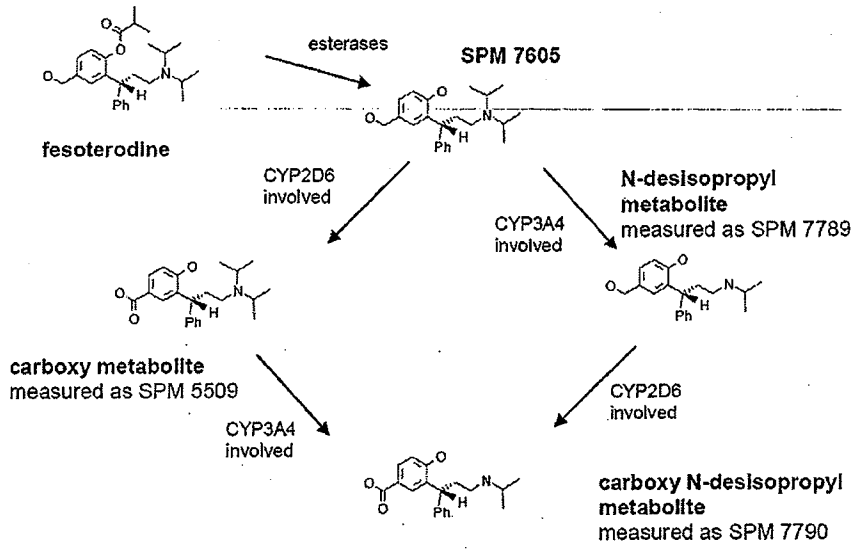
The figure below depicts the proposed metabolic pathway for fesoterodine based on in vitro studies. Examination of metabolite profiles following CYP2D6 inhibition (e.g., CYP2D6 PM in study SP 565) and CYP3A4 induction (SP 683) support the proposed pathway.

Data from study SP565 showed that plasma concentrations, C_{max} and AUC increased up to 4 times for SPM 7789 and about 2 times for SPM 7605 in CYP2D6 poor metabolizers. The same parameters decreased by a factor of about 2 for the metabolites SPM 7790 and SPM 5509. These data are consistent with the proposed metabolic pathway.

The data collected on renal elimination show a similar pattern compared to the plasma results: the excreted amounts for SPM 5509 and SPM 7790 decreased by a factor of about 2 comparing poor with extensive metabolizers. The excreted amounts for SPM 7605 and SPM 7789 increased by a factor of about 2 and 8.

There may be additional pathway for the conversion of SPM 7605 to SPM 5509 other than CYP2D6 since the plasma concentrations of SPM 5509 in PM are still about half of that in EM.

Figure 5: metabolic pathway of fesoterodine



The following 3 tables and 3 figures show the PK parameters and profiles for metabolites beyond SPM 7605.

Table 13: PK parameters of SPM 5509 in plasma following 8 mg fesoterodine in CYP2D6 PM and EM under fasting and fed states (SP565)

Fesoterodine dose	N	$AUC_{(0-t)}$ [ng*h/mL] mean±SD	C_{max} [ng/mL] mean±SD	t_{max} [h] median (range)	$t_{1/2}$ [h] median (range)
Extensive metabolizers					
8mg fasting	16	209±55.1	14.8±4.33	5.00 (3.0-6.0)	8.39 (3.8-11.5)
8mg fed	16	243±39.4	19.4±3.76	5.00 (4.0-10.0)	5.66 (3.9-8.8)
Poor metabolizers					
8mg fasting	8	117±14.2	7.53±1.00	5.00 (4.0-8.0)	8.62 (5.9-11.1)
8mg fed	8	126±14.3	9.11±1.81	5.50 (4.0-10.0)	6.87 (5.0-8.9)

Figure 6: Mean SPM 5509 concentration following 8 mg fesoterodine in CYP2D6 PM and EM under fasting and fed states (SP565)

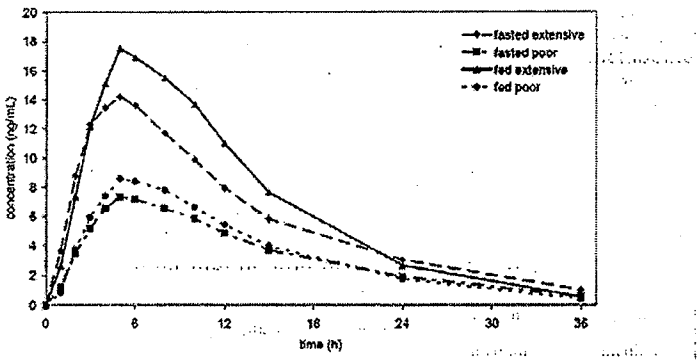


Table 14: PK parameters of SPM 7789 in plasma following 8 mg fesoterodine in CYP2D6 PM and EM under fasting and fed states (SP565)

Fesoterodine dose	N	$AUC_{(0-t)}$ [ng*h/mL] mean±SD	C_{max} [ng/mL] mean±SD	t_{max} [h] median (range)
Extensive metabolizers				
8mg fasting	16	1.23±1.33	0.25±0.15	5.00 (2.0-36.0)
8mg fed	16	2.07±1.73	0.33±0.17	5.00 (2.0-36.0)
Poor metabolizers				
8mg fasting	8	6.82±3.14	0.64±0.22	5.00 (4.0-8.0)
8mg fed	8	7.13±2.38	0.63±0.15	5.00 (3.0-10.0)

Figure 7: Mean SPM 7789 concentration following 8 mg fesoterodine in CYP2D6 PM and EM under fasting and fed states (SP565)

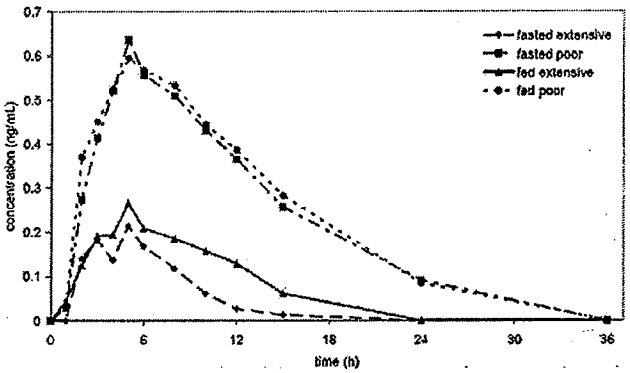
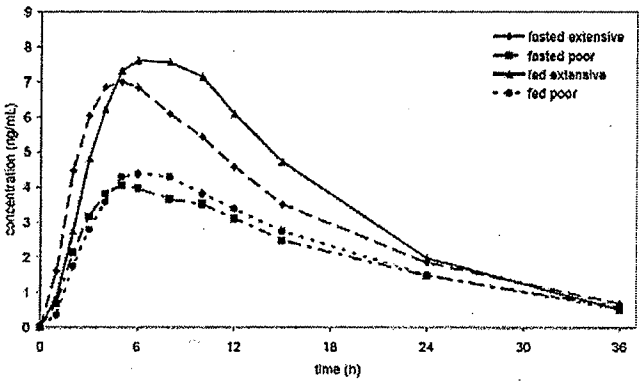


Table 15: PK parameters of SPM 7790 in plasma following 8 mg fesoterodine in CYP2D6 PM and EM under fasting and fed states (SP565)

Fesoterodine dose	N	$AUC_{(0-t)}$ [ng*h/mL] mean±SD	C_{max} [ng/mL] mean±SD	t_{max} [h] median (range)	$t_{1/2}$ [h] median (range)
Extensive metabolizers					
8mg fasting	16	115±34.7	7.47±2.59	5.00 (3.0-6.0)	9.07 (5.8-11.5)
8mg fed	16	130±34.0	8.61±2.21	6.00 (4.0-15.0)	6.94 (5.0-9.8)
Poor metabolizers					
8mg fasting	8	76.0±25.6	4.27±1.25	5.00 (4.0-8.0)	10.2 (8.3-15.2)
8mg fed	8	79.5±23.9	4.72±1.92	6.00 (5.0-12.0)	9.58 (6.5-11.6)

Figure 8: Mean SPM 7790 concentration following 8 mg fesoterodine in CYP2D6 PM and EM under fasting and fed states (SP565)



Study SP683 (rifampicin interaction) also examined the metabolic profile of metabolites of SPM 7605 and showed that following induction of the CYP3A4 pathway, plasma SPM 5509 levels decreased by 2.8-fold while both plasma SPM7789 and SPM7790 increased. SPM7790 increased by about 3-fold while SPM7789 increased by about 1.5-fold (figures 9 - 11). These shifts in metabolites are consistent with the proposed metabolic pathway for SPM 7605.

Figure 9: Plasma concentration of SPM 5509 (arithmetic mean) following 8 mg fesoterodine (SP683)

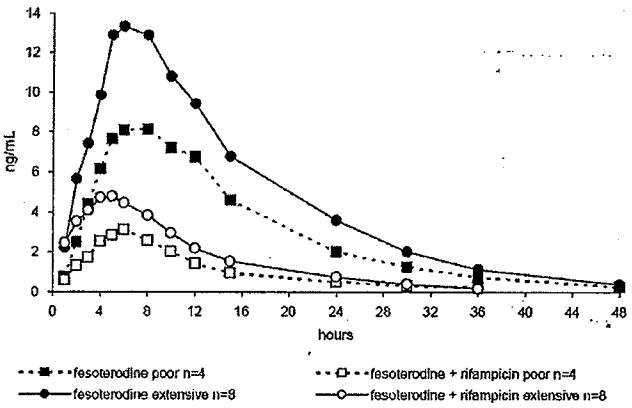


Figure 10: Plasma concentration of SPM 7789 (arithmetic mean) following 8 mg fesoterodine (SP683)

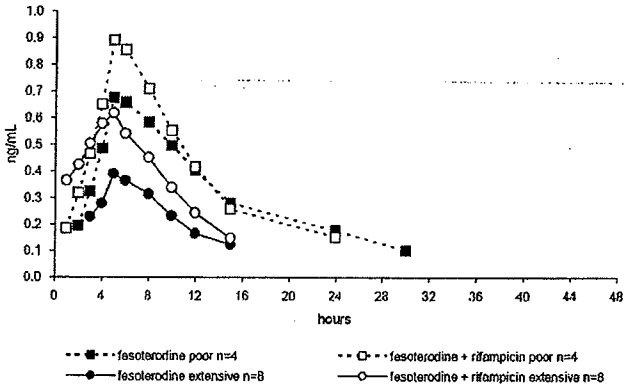
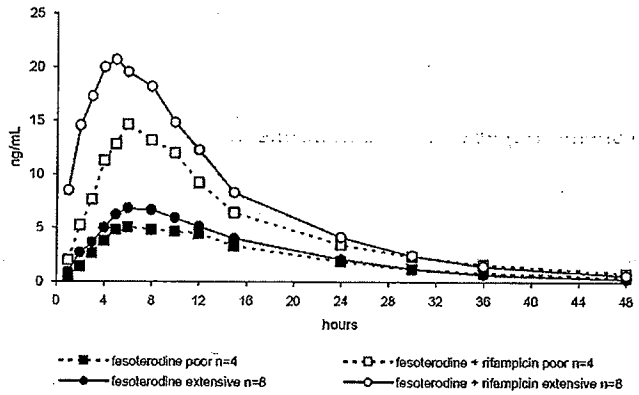


Figure 11: Plasma concentration of SPM 7790 (arithmetic mean) following 8 mg fesoterodine (SP683)



In vitro studies also support the roles of CYP2D6 and CYP3A4 in the metabolism of SPM 7605. Please see the Pharmacology/Toxicology review by Dr. Laurie McLeod for details.

2.2.5 What are the routes of excretion for fesoterodine?

Fesoterodine is excreted as it metabolites mainly in the urine (70%) with a minor portion in the feces (7%) at 96 hours after dosing.

At up to 36 hours post dosing about 63 – 68% of applied dose was excreted in the urine as one of the 4 metabolites (table 16). Additional renal excretion was possible since the cumulative excretion did not clearly reach a plateau at 36 hours. A mean renal excretion of 69.7% was observed in study SP 567 when collected up to 96 hours. Excretion in feces was low at about 6.8%.

Table 16: cumulative renal excretion (% of dose applied) following 8 mg fesoterodine in CYP2D6 PM and EM under fasting and fed states as measured up to 36 hours post dosing (SP565)

	n	SPM 7605	SPM 5509	SPM 7789	SPM 7790	SUM
Extensive metabolizers						
8mg fasting	16	14.5 ± 4.86	33.6 ± 6.60	0.6 ± 0.55	19.7 ± 5.98	68.4
8mg fed	15	17.3 ± 4.71	40.8 ± 9.29	0.8 ± 0.59	23.5 ± 7.27	82.4
Poor metabolizers						
8mg fasting	8	27.7 ± 9.39	19.5 ± 3.66	2.8 ± 0.91	13.2 ± 1.91	63.2
8mg fed	8	31.2 ± 8.53	20.6 ± 2.94	3.0 ± 0.65	14.0 ± 4.90	68.8

Table 17: Amount (% of dose) excreted into urine and feces (arithmetic mean) up to 96 hours following 8mg fesoterodine dosing (SP 567).

Treatment		Renal elimination (n=11)	Elimination in feces (n=11)	Total elimination (n=11)
8mg fesoterodine SR tablet	SPM 7605	16.22	4.41	20.63
	SPM 5509	33.74	1.44	35.18
	SPM 7789	1.27	0.22	1.49
	SPM 7790	18.48	0.77	19.25
	Total[1]	69.71	6.84	76.55

2.2.6 What design features of PK and clinical efficacy trials are used to support dosing?

The proposed dosing of fesoterodine is 4 or 8 mg ER once daily. The PK of fesoterodine at these dose levels and once daily schedule has been comprehensively evaluated in phase 1, 2, and 3 studies.

Firstly, the PK of single dose and multiple daily dose of 4 or 8 mg fesoterodine was evaluated in several phase 1 studies as described in section 2.2.1.

Secondly, the once daily regimen was also evaluated in phase 2 studies (SP 582 and SP 668) at 4, 8, and 12 mg dose levels for preliminary efficacy and safety, where sparse PK sampling was also done. The preliminary efficacy and safety data from these phase 2 studies suggested that 4 and 8 mg doses of fesoterodine were appropriate be tested in phase 3.

Population PK modeling was conducted to describe the data and determine possible covariates. The population PK parameter estimates are listed in table 18. Study SP582 did not support inclusion of any covariate. In study SP668, the only covariate identified was CYP2D6 status on V/f but it only reduced the inter-individual variability (IIV) slightly from 44% to 41%. The final model in both phase 2 studies still had high residual random error of 46 – 53% that cannot be explained by the model. This high level of uncertainty partly contributed to a decision to obtain sparse sampling in one of the phase 3 trials in order to improve the model.

Finally, the proposed dose regimens were directly examined in two safety and efficacy phase 3 trials SP 583 and SP 584. Both 4 and 8 mg dose were determined to be safe and effective in the Medical Officer's review.

Study SP 584 also included sparse plasma sampling for population PK modeling. A population PK model was developed to describe the data and suggested that CYP2D6 status was a covariate for total body clearance in addition to height, alkaline phosphatase concentration, and GGT (gamma glutamyl transferase) concentration. The model predicts that CL/f is about 30% less in PM compared to EM (84.6 L/h vs. 111.9 L/h). This is similar to the apparent CL/f after 8 mg fesoterodine in study SP 565 (55.6 L/h and 107.2 L/h for PM and EM, respectively). Based on the model, alkaline phosphatase and GGT concentrations played a minor role while extreme body heights may affect clearance. The inclusion of body height as a covariate on clearance is not supported by physiology and perhaps should be removed. The covariate for V/f was body weight (model assumption of weigh normalized volume of distribution) with a minor influence by total bilirubin. The PK parameters were only roughly estimated as the residual error of the final model was high at 54%. Part of the reason for high residual variability might be due to the simplistic model (1 compartment with first order absorption and elimination) used and may not capture the true physiology and improved disease progression in these patient population. However, since a comprehensive set of phase 1 studies evaluating a number of intrinsic and extrinsic factors is available, further fine tuning population PK models is not needed.

Table 18: Final estimates from the 3 trials. Additional parameters can be found in Appendix 4.2.2.

Trial	CL/f (L/h)	Ke (h^{-1})/IIV%	V/f (L)/IIV %	Residual random error
SP 582	79.6[a]	0.0622/44%	1280/16%	53%
SP 668	113.8[a] EM 84.6[a] PM	0.0694/27%	1640/41% EM 1219/41% PM	46%
SP 584	111.9 EM 84.6 PM	0.0637[b] EM 0.048[b] PM	1758	54%

[a] calculated from Ke*V/f, [b] calculated from CL/V

In conclusion the proposed doses of 4 and 8 mg fesoterodine once daily have been directly examined for PK properties and safety and efficacy. Population PK modeling to determine covariates had limited success since there were still high residual variability in the final models. The main covariate determined by population PK was CYP2D6 genotype, which is in agreement with results from phase 1 studies of CYP2D6 PM and EM subjects. Sponsor did not conduct analysis to determine the lowest effective dose. However, since both the 4 and 8 mg doses were considered safe by the medical reviewer, the need to obtain more data at doses below 4 mg is not warranted.

2.2.7 What are the characteristics of dose-response relationships?

Potential dose-response relationship was evaluated by examining the safety and efficacy results of 4 and 8 mg fesoterodine doses in the primary efficacy and safety studies SP 583 and SP 584. Phase 2 data, while useful in planning the phase 3 trials during drug development, is surpassed by more comprehensive data from the phase 3 trial and therefore not considered in this evaluation.

In study SP-583, a total of 1135 subjects were randomized and 1132 were treated: 279 with placebo, 265 with fesoterodine 4mg/day, 276 with fesoterodine 8mg/day and 283 with tolterodine 4md/day. Most subjects (>80% in any treatment group) completed full 12 weeks of treatment.

Most of subjects (81%) were females with a mean age of 57 years and an overall age range of 19 to 86 years.

In study SP-584 a total of 836 subjects were randomized and 832 subjects treated: 266 with placebo, 267 with fesoterodine 4mg/day and 267 subjects with fesoterodine 8mg/day. Most subjects (>80% in any treatment group) completed full 12 weeks of treatment. Majority (76%) of subjects were females, mean age of 59 years and an overall age range of 21 to 91 years. A total of 9% of subjects were poor metabolizers for CYP2D6.

Efficacy:

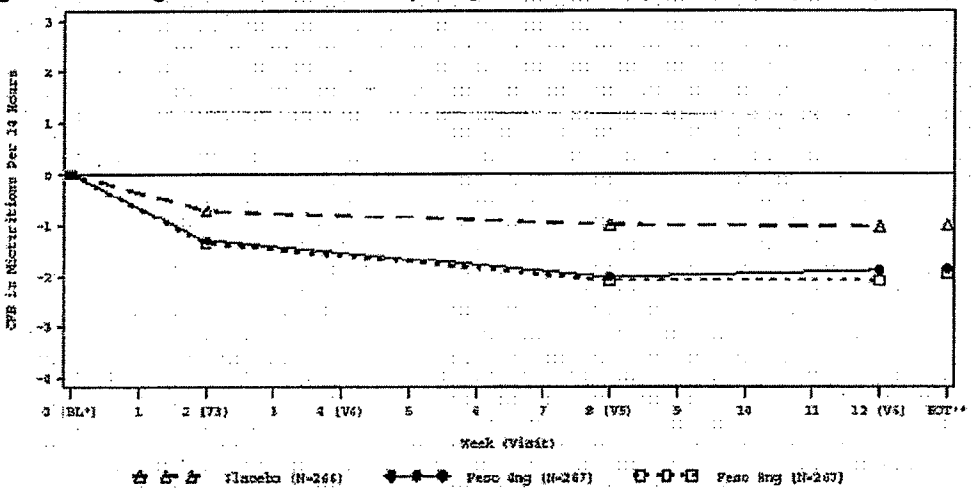
The primary endpoints were (1) Number of Micturitions per 24 hours and (2) Urge Incontinence episodes per 24 hours. A key secondary endpoint considered by the Medical Officer was volume voided. A summary of the results on these 3 endpoints are shown below (adapted from MO's draft review – statistical analysis was not yet finalized at the time of this review).

Table 19: Micturition per 24 hours

Micturitions per 24 hours	SP 583			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
Mean (SD), sample size reflects number of subjects at baseline Adapted from Medical Officer's review						

Number of micturitions at baseline was similar among the treatment groups in both studies. Fesoterodine groups were significantly better than placebo and fesoterodine 8 mg was slightly better than fesoterodine 4 mg. However, the additional improvement of 8 mg over 4 mg is small, improvement of 0.2 and 0.08 micturition per day in SP 583 and SP 584, respectively. These further improvements represent 28% and 9.5% over the improvements achieved in fesoterodine 4 mg vs. placebo in SP 583 and SP 584, respectively.

Figure 12: Change from baseline in frequency of micturition per 24 hours (SP 584)



The mean change from baseline over time was similar between the 2 fesoterodine groups.

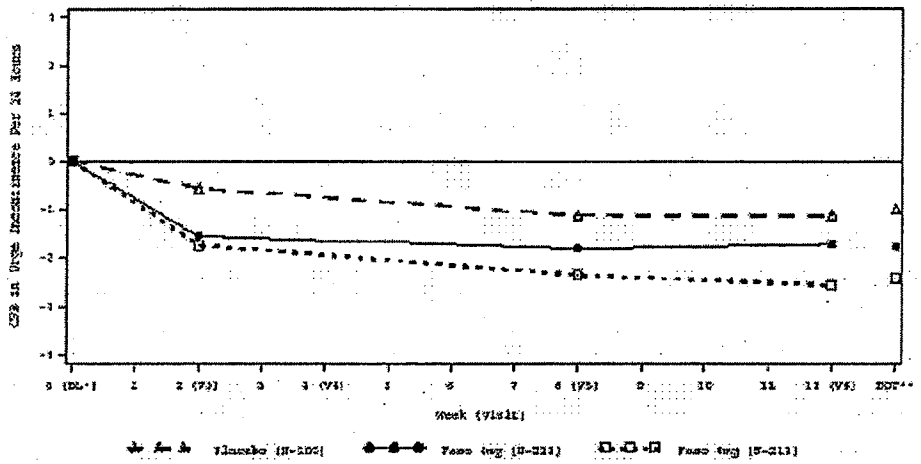
Table 20: Incontinence episode per 24 hours

	SP 583			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
Mean (SD), sample size reflects number of subjects at baseline Adapted from Medical Officer's review						

Number of incontinence episodes at baseline was similar among the treatment groups in both studies. Fesoterodine groups were significantly better than placebo and fesoterodine 8 mg was slightly than fesoterodine 4 mg. The further improvement of fesoterodine 8 mg was modest in SP 583 (0.21 episode per 24 hours) and more pronounced in SP 584 (0.65 episode per 24 hour). These further improvements suggest a dose response relationship since they are sufficiently large relative to the improvements of 0.86 and 0.77 observed for fesoterodine 4 mg vs. placebo in SP 583 and SP 584, respectively. These further improvements represent 24% and 84% over the improvements achieved in fesoterodine 4 mg vs. placebo in SP 583 and SP 584, respectively.

Figure 13

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

The effect was similar between the 2 fesoterodine groups at week 2 but a separation was seen at week 8 and 12 due to continued increase in improvement in the 8 mg dose group.

Table 21: Voided volume

	SP 583			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 for change from baseline vs. placebo		P=<0.001	P<0.001		P=0.15	P<0.001
Mean (SD), sample size reflects number of subjects at baseline Adapted from Medical Officer's review						

There appears to be a greater improvement in the fesoterodine 8 mg group relative to the 4 mg group. The additional improvements represents 38% and 180% of the improvement observed in fesoterodine 4 mg vs. placebo in SP 583 and SP 584, respectively.

Overall, fesoterodine 4 and 8 mg/day dose appears to exhibit a positive dose-response relationship. The further improvement of the 8 mg dose was modest (28% and 9.5%) for the Number of Micturitions per 24 hours endpoint and more substantial in the other primary endpoint

of Urge Incontinence episodes per 24 hours (24% and 84%) as well as the secondary endpoint volume voided (38% and 180%).

Safety:

The safety effect of fesoterodine was evaluated by the integration of all 4 phases 2 and 3 trials (pool S1). The table below shows the common adverse events. There appear to be a dose dependent increase in dry mouth and constipation. Other adverse effects were similar among placebo and fesoterodine 4 mg and 8 mg dose groups.

Table 22

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

Table 23 shows the effect of heart rate of all phase 2 and 3 studies (Pool S1) or only the phase 3 studies (Pool S5). The data show that fesoterodine caused a dose dependent increase in heart rate.

Table 23

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

In conclusion there was a positive dose-response relationship with incidence of dry mouth and constipation and increased heart rate for fesoterodine doses of 4 mg and 8 mg/day. These adverse effects may be related to the pharmacological effects of fesoterodine. The rates of other common adverse effects were low and similar to placebo.

2.2.8 What is the linearity or nonlinearity of dose-concentration relationship for the ER formulation?

Data from 3 studies (SP565, SP877, and SP686) are available to evaluate dose proportionality of fesoterodine (as the active metabolite SPM 7605). Study SP 565 showed dose proportionality among 4, 8, and 12 mg doses (table 8 in section 2.2.1.3). Study SP 877 also showed dose proportionality between 4 and 8 mg tablets of formulation F with dose normalized 4mg/8mg ratios (and 90% CI) for AUC and C_{max} of 0.99 (0.91 – 1.09) ng/ml*h and 0.96 (0.86 – 1.07) ng/mL, respectively. In study SP686, doses of 4 and 28 mg/day for 3 days (a 7-fold different) were given to healthy volunteers. The mean AUC and C_{max} increased by 8.5- and 7.8-fold, respectively, suggesting linear dose proportional increase in exposure is maintained up to 28 mg/day dose.

In conclusion the ER formulation of fesoterodine exhibits dose proportionality in the range of 4 – 12 mg and potentially up to 28 mg.

2.2.9 What is the effect of fesoterodine on QT interval?

The effect of fesoterodine was evaluated in study SP 686 using 4 mg and 28 mg once daily for 3 days. This study was of parallel design and compared fesoterodine 4 mg, 8 mg, and placebo, with 400 mg/day moxifloxacin as the positive control.

The results showed that the assay was sensitive by positive signal from moxifloxacin 400 mg/day (maximum mean placebo subtracted time-matched QTcF of 15.5 msec (upper 95% CI 19.6 msec)).

Sponsor's analysis of time-average data showed that fesoterodine 4 and 28 mg slightly decreased QTc interval and did not differ from placebo. Mean time-averaged QTcF decreased by 4.7, 4.6, and 5.0 ms after 3 days of treatment with placebo, 4mg fesoterodine, and 28mg fesoterodine, respectively. By time matched analysis of baseline subtracted data, both doses of fesoterodine and placebo generally had time matched QTcF that were less than at baseline.

We also conducted time-matched baseline-corrected and placebo-corrected (ddQTc) analysis on QTcF and QTcI. The placebo group mean at each time point was used for placebo correction because of the parallel study design. The results showed no significant increase in QTc (i.e., upper 95% CI ≤ 10 msec) with 4 mg/day fesoterodine at all timepoints. The supratherapeutic dose of 28 mg/day showed positive increase (7.0 msec, upper 95% CI 11.1 by QTcF) at 3 hour post dose on Day 3. It is not clear if this is a true positive effect since the 2 hour and 4 hour time points (i.e., immediately before and after) both have negative mean QTc effect with upper 95% CI <4 msec. The positive effect at 3 hour time point might be due mainly to a sharp decrease in QTc of the placebo group at that particular time point. Additionally, the mean T_{max} observed in this study was at 4.1 hour for the 28 mg dose, i.e., later than the time of positive ddQTcF at 3 hour. Concentration ddQTc response analysis indicated no significant effect of fesoterodine 4 and 28 mg on either QTcF or QTcI. These data together suggest there is no significant effect of fesoterodine up to 28 mg/day on prolonging the QTc interval.

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 fesoterodine treatment groups.

Fesoterodine did have a significant effect on increasing heart rate, which was anticipated. The number of subjects with a heart rate increase of >25% and >100bpm was higher in the fesoterodine treatment groups (16.9%, 39.1%, and 76.5% in the placebo, 4mg/day, and 28mg/day fesoterodine groups, respectively) due to the pharmacological effect of anticholinergics to increase heart rate.

In conclusion, data from this thorough QT study did not support an effect of 4 and 28 fesoterodine on prolonging the QTc interval. For further details, please see the study review at the end of this QBR.

Review note: This NDA with a thorough QT study was submitted to the Agency before the Interdisciplinary Review Team for QT (IRT-QT) was formed. At the time of this review, December 5, 2006, the Pharmacometrics team has not presented the results of this QT study to the IRT-QT. The Division of Clinical Pharmacology III and the Division of Reproductive and Urologic medical review team find that no significant effect on QT prolongation at doses of 4 and 28 mg/day.

2.3 Intrinsic Factors

2.3.1 What is the effect of sex and age on fesoterodine PK?

The effect of sex and age on pharmacokinetics of 8 mg fesoterodine (SPM 8272) (2 x 4 mg ER tablets) single dose was examined in study SP570. The trial was designed as a randomized, double-blind, placebo- controlled, parallel group trial with oral single dose administration of 8 mg SPM 8272 or placebo to 16 healthy young male, 16 healthy elderly male and16 healthy elderly female subjects (of each group, 12 subjects received active substance, 4 placebo).

The age in year distribution is listed in the table below.

Table 24: Age distribution for study SP570

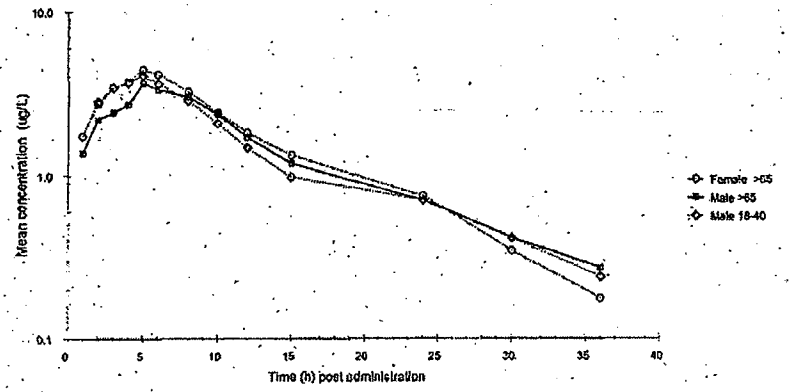
	Young males		Elderly males		Elderly females	
	SPM 8272	Placebo	SPM 8272	Placebo	SPM 8272	Placebo
N	12	4	12	4	12	4
Mean	29.5	30.0	67.1	69.5	68.0	68.3
Minimum	21	18	65	66	65	67
Maximum	36	38	69	73	77	70

The exposure (AUC and C_{max}) to SPM 7605 were similar among the 3 groups. Total body clearance and T_{max} were also similar. There were slightly lower renal clearance values in both older female and male groups compared to young males. This may be related to the lower glomerular filtration rate in older population. Table 25 lists the calculated PK parameters for all 3 groups. Figure 14 shows the similarity in concentration vs. time profiles for all 3 subject groups following 8 mg fesoterodine.

Table 25: PK parameters following single-dose 8 mg fesoterodine

	Young males	Elderly males	Elderly females
AUC(0-t_z) [h*µg/l]	48.9 ± 29.1	48.0 ± 25.0	54.1 ± 27.9
AUC(0-t_z)$_{norm}$ [h*(µg/l) / (mg/kg)]	511.2 ± 332.8	468.4 ± 206.8	472.2 ± 263.3
C_{max} [µg/l]	4.1 ± 2.1	3.8 ± 1.7	4.6 ± 2.3
$C_{max,norm}$ [(µg/l) / (mg/kg)]	42.8 ± 24.0	37.2 ± 13.8	39.9 ± 21.8
AUC(0-∞) [h*µg/l]	52.0 ± 31.5	51.8 ± 26.1	56.0 ± 28.8
AUC(0-∞)$_{norm}$ [h*(µg/l) / (mg/kg)]	543.0 ± 355.8	506.2 ± 214.3	488.5 ± 269.0
CL/f [l/h]	197.2 ± 90.3	183.1 ± 70.2	174.1 ± 71.9
MRT [h]	10.8 ± 0.71	11.4 ± 0.98	10.5 ± 1.7
t_{max} [h] (median (range))	5 (3 – 6)	5 (4 – 8)	5.5 (3 – 6)
$t_{½}$ [h]	9.2 ± 1.9	9.4 ± 2.1	7.0 ± 2.2
Ae_{ur} [mg]	0.682 ± 0.278	0.523 ± 0.246	0.549 ± 0.226
CL_{ren} [l/h]	14.35 ± 2.92	10.48 ± 3.03	10.37 ± 2.41

Figure 14: Mean of SPM 7605 concentrations (8 mg single dose) in study SP570



Population PK modeling in SP584 did not find age or sex to be a covariate for clearance or volume of distribution, supporting a lack of influence of these intrinsic factors on the PK of fesoterodine.

In conclusion the exposure to SPM 7605 was very similar among groups of young males, elderly males, and elderly females. No dose adjustment for age between young adults and the elderly is needed. Additionally, no dose adjustment is needed for difference in sex.

2.3.2 What is the effect of hepatic impairment on fesoterodine PK?

The effect of moderate liver impairment was examined in study SP569. The study was carried out as a two-site, open-label, parallel-group comparison of the plasma and urinary PK of SPM 7605 and its main metabolites after a single oral dose of 8mg fesoterodine ER in subjects with moderate hepatic cirrhosis (Child- Pugh stage B), compared with age-, bodyweight- and body mass index (BMI)-matched healthy subjects (n=8 each, 1 was CYP2D6 PM). Note: since both treatment groups contained 1 CYP2D6 PM subject each, the PK analysis did not separate EM and PM.

This study (n=8, parallel study) on the effects of moderate liver impairment showed that AUC(0-tz) was increased 2.13 fold (95% CI 1.48 – 3.05) and C_{max} increased 1.39 fold (95% CI 1.01 – 1.90) in subjects with moderate hepatic impairment (table 28).

Figure 15: Plasma PK profile of SPM 7605 (arithmetic mean) following 8 mg fesoterodine in healthy subjects or subjects with moderate hepatic cirrhosis

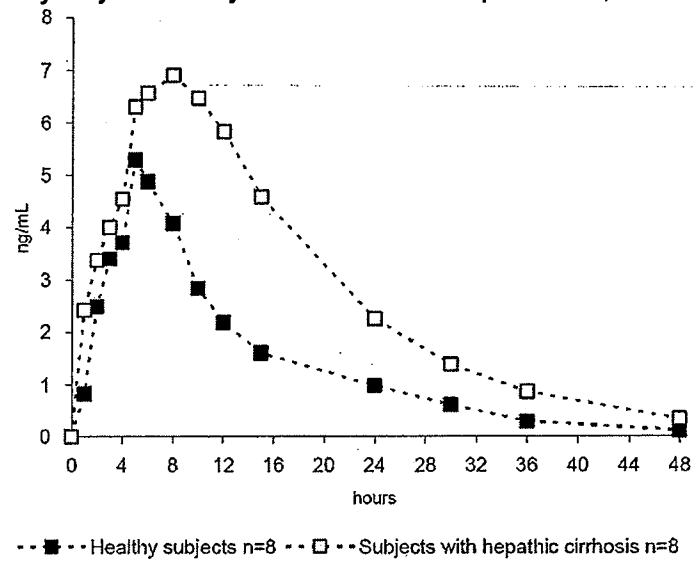


Table 26: Descriptive statistics of the main PK parameters of SPM 7605 in healthy subjects (n=8)

	unit	arith. mean	arith. SD	geom. mean	geom. CV %	median	min.	max.
$AUC_{(0-tz)}$	ng/mL*h	67.20	27.06	62.22	45.52	60.01	27.72	108.70
$AUC_{(0-48)}$	ng/mL*h	67.16	27.13	62.11	45.93	60.01	27.36	108.70
$AUC_{(0-\infty)}$	ng/mL*h	68.72	27.83	63.53	46.11	61.45	27.89	112.38
C_{max}	ng/mL	5.45	1.66	5.20	35.12	5.32	2.63	7.77
$t_{1/2}$	h	8.36	1.53	8.24	18.74	8.5	6.17	10.81
A_e	µg	819.49	356.90	740.32	54.42	842.7	335.42	1345.43

Table 27: Descriptive statistics of the main PK parameters of SPM 7605 in subjects with moderate hepatic cirrhosis (n=8)

	unit	arith. mean	arith. SD	geom. mean	geom CV %	median	min.	max.
$AUC_{(0-tz)}$	ng/mL*h	134.12	24.62	132.05	19.32	138.82	97.01	162.82
$AUC_{(0-48)}$	ng/mL*h	134.12	24.62	132.05	19.32	138.82	97.01	162.82
$AUC_{(0-\infty)}$	ng/mL*h	138.95	24.46	136.92	18.86	146.96	99.91	165.43
C_{max}	ng/mL	7.39	1.76	7.21	24.02	6.95	5.42	9.76
$t_{1/2}$	h	8.85	2.10	8.62	24.70	8.93	5.96	11.91
A_e	µg	1891.68	301.06	1871.76	15.49	1810.22	1486.58	2452.12

Table 28: Explorative estimated ratios for cirrhosis:healthy for main PK parameters of SPM 7605

	ratio	95% CI
$AUC_{(0-tz)}$	2.126	1.480 - 3.053
$AUC_{(0-48)}$	2.122	1.481 - 3.041
$AUC_{(0-\infty)}$	2.155	1.501 - 3.095
C_{max}	1.387	1.012 - 1.900
λ_z	0.955	0.757 - 1.205
$t_{1/2}$	1.047	0.830 - 1.320
A_e	2.528	1.689 - 3.785

Table 29 shows the PK parameters for metabolites beyond SPM 7605. Exposure to SPM 5509 and SPM 7790 decreased while exposure to SPM 7789 increased in subjects with moderate hepatic cirrhosis. It was interesting to see that SPM 7789 levels, thought to be formed via CYP3A4, actually increased (AUC and C_{max} ratios (95% CI) of 3.6 (1.0 – 12.6) and 1.5 (0.8 – 2.8), respectively) rather than decreased, as would be expected if CYP3A4 activity were decreased. The relative fold increase of SPM 7789 was higher than that observed for SPM 7605 but when the smaller absolute amount of SPM 7789 was taken into account, the absolute increase in AUC and C_{max} of SPM 7789 were small and the resulting exposure was similar to that observed in CYP2D6 PM subjects in other studies. Therefore this increase in SPM 7789 by itself should not pose a safety concern.

The metabolite pattern in patients with moderate hepatic impairment is similar to that observed in CYP2D6 PMs, where SPM 7605 and 7789 increased while SPM 5509 and 7790 decreased. This suggests that the hepatic cirrhosis patients had depleted CYP2D6 but normal CYP3A4.

Table 29: PK parameters for all 4 metabolites following 8 mg fesoterodine in healthy subjects and subjects with moderate hepatic cirrhosis

			Healthy subjects (n=8)		Subjects with hepatic cirrhosis (n=8)	
		unit	geom. mean	geom. CV %	geom. mean	geom. CV %
SPM 7605	$AUC_{(0-tz)}$	ng/mL*h	62.22	45.52	132.05	19.32
	C_{max}	ng/mL	5.20	35.12	7.21	24.02
	$t_{1/2}$	h	8.24	18.74	8.62	24.70
	A_e	mcg	740.32	54.42	1871.76	15.49
SPM 5509	$AUC_{(0-tz)}$	ng/mL*h	200.21	31.16	107.35	44.35
	C_{max}	ng/mL	13.40	36.84	4.65	56.30
	$t_{1/2}$	h	8.49	20.82	9.82	26.09
	A_e	mcg	1628.29	36.86	760.52	52.58
SPM 7789	$AUC_{(0-tz)}$	ng/mL*h	2.08	176.05	7.21	119.45
	C_{max}	ng/mL	0.30	61.03	0.44	69.86
	$t_{1/2}$	h	0	0	0	0
	A_e	mcg	52.02	87.91	106.37	52.97
SPM 7790	$AUC_{(0-tz)}$	ng/mL*h	106.19	33.33	61.18	68.13
	C_{max}	ng/mL	6.40	42.28	2.58	72.44
	$t_{1/2}$	h	9.57	22.20	11.87	27.02
	A_e	mcg	952.08	29.87	415.29	72.01

In conclusion moderate liver impairment increased SPM 7605 C_{max} and AUC by 1.4 and 2.1 fold, respectively. SPM 7789 C_{max} and AUC increased by 1.5 and 3.6 fold, respectively, but should not be a safety concern since the absolute amount was still small and comparable to those observed in CYP2D6 PM subjects. Exposure to SPM 5509 and SPM 7789 decreased. No dose adjustment is needed for moderate hepatic impairment due to the small increase in exposure, particularly the low 1.4-fold increase in C_{max}.

Severe hepatic impairment was not examined. Sponsor proposed that the label states in the precaution section that fesoterodine is not recommended for use in this patient population. This reviewer concurs since the majority of SPM 7605 are excreted as metabolic metabolites and significant increase in SPM 7605 exposure was observed when both CYP2D6 and CYP3A4 pathways was blocked (section 2.4.2), a condition that could occur in severe hepatic impairment.

2.3.3 What is the effect of renal impairment on fesoterodine PK?

The effect of mild, moderate, and severe renal impairment on the PK of fesoterodine was examined in study SP568. This was an open-label, group comparison, single dose trial with an oral dose of 4 mg fesoterodine in subjects with mild, moderate, or severe renal impairment compared with healthy subjects. The subjects received 1 ER tablet containing 4mg fesoterodine fumarate.

The subjects were assigned to 4 groups (N=8) according to the creatinine clearance values. Group 1: healthy controls, Group 2: mild renal impairment, Group 3: moderate renal impairment, Group 4: severe renal impairment. Subjects were not stratified by CYP2D6 status. However, genotyping data indicate there was one PM subject in each of the mild and severe renal impairment groups.

Renal impairment increased exposure to SPM 7605. Exposure to SPM 7605 increased in parallel to the stages of severity of renal impairment with mean AUC increases of 1.6-, 1.8-, and 2.3-fold for mild, moderate, and severe renal impairment, respectively (table 30).

Table 30: Ratio between groups for SPM 7605 following 4 mg of fesoterodine

Parameter	LS-Means [90% CI]		
	Mild vs healthy	Moderate vs healthy	Severe vs healthy
C_{max}	1.35 [0.997; 1.815]	1.48 [1.095; 1.993]	2.03 [1.508; 2.745]
$AUC_{(0-tz)}$	1.59 [0.972; 2.597]	1.83 [1.120; 2.993]	2.33 [1.422; 3.802]

Table 31 shows the PK parameters for SPM 7605 for all groups. AUC(0-tz) and C_{max} were clearly higher in the subjects with renal impairment and increased with the severity of renal impairment. Values for AUC(0-tz) were 1.6-fold higher and values for Cmax were 1.3 fold higher in subjects with mild renal impairment compared to healthy subjects. In subjects with moderate renal impairment, values for AUC(0-tz) were 1.8-fold higher and values for Cmax were 1.5 fold higher compared to healthy subjects. In subjects with severe renal impairment, values for AUC(0-tz) were 2.3-fold higher and values for Cmax were 2.0-fold higher compared to healthy subjects.

Mean terminal half-life ($t_{1/2}$) of SPM 7605 was comparable across the 4 trial groups. The mean $t_{1/2}$ appear slightly higher in the moderate and severe groups but were not significantly different and were similar to $t_{1/2}$ reported in other studies. $T_{1/2}$ is probably not very sensitive to change in drug clearance since a previous study indicates that it is absorption rate limited. There was no difference in T_{max} among the 4 groups. The amount of SPM 7605 excreted into urine (Aeur) decreased with increasing severity of renal impairment. The renal clearance (CLren) was approximately 80% lower in subjects with severe renal impairment compared to healthy subjects. The total body clearance (CL/f) was approximately 56% lower in subjects with severe renal impairment.

Table 31: PK parameters of SPM 7605 following fesoterodine 4 mg in healthy (group 1), mild (group 2), moderate (group 3), or severe (group 4) impairment of renal function.

Parameter	Unit	Geometric mean (CV%)			
		Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)
C_{max}	ng/mL	1.90 (53.5)	2.56 (32.3)	2.81 (29.6)	3.87 (25.0)
$C_{max,norm}$	ng/mL*kg	138.8 (54.1)	214.4 (26.8)	226.5 (31.0)	304.6 (19.5)
$AUC_{(0-tz)}$	ng/mL*h	19.11 (110.9)	30.35 (54.9)	34.97 (45.3)	44.43 (29.5)
$AUC_{(0-tz)norm}$	ng/mL*h*kg	1395.4 (106.3)	2544.7 (46.8)	2820.3 (46.7)	3497.8 (29.5)
$t_{½}$	h	5.79 (58.8)	6.11 (31.9)	7.31 (24.5)	7.15 (32.3)
t_{max} [a]	h	5.0 (2-6)	6.0 (4-8)	6.0 (1-6)	5.0 (3-6)
Ae_{ur}	µg	278.89 (77.2)	235.21 (69.2)	160.92 (50.7)	111.53 (26.7)
CL_{ren}	L/h	14.39 (30.1)	7.70 (57.0)	4.05 (58.6)	2.56 (16.5)
CL/f	L/h	201.37 (107.3)	128.70 (54.7)	111.90 (45.3)	88.59 (29.9)

[a] median (range)

The fraction unbound was slightly lowered in all renally impaired subjects with range of 0.43 to 0.45 compare to 0.54 in healthy subjects (table 32). However, the ratios of unbound PK parameters were similar to that observed with total SPM 7605.

Table 32: Fraction unbound and PK parameters of fraction unbound of SPM 7605

Parameter	Unit	Geometric mean (CV%)			
		Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)
f_u	fraction	0.54 (8.4)	0.45 (11.4)	0.43 (9.0)	0.43 (15.6)
$AUC_{(0-tz)u}$	ng/mL*h	10.34 (100.7)	13.59 (60.2)	15.07 (43.0)	19.05 (34.6)
$AUC_{(0-tz)u,norm}$	ng/mL*h*kg	754.8 (96.0)	1138.9 (52.2)	1215.1 (41.7)	1499.7 (29.0)
$C_{max,u}$	ng/mL	1.03 (45.1)	1.14 (35.0)	1.21 (28.9)	1.66 (35.2)
$C_{max,u,norm}$	ng/mL*kg	75.1 (45.8)	96.0 (29.5)	97.6 (26.5)	130.6 (25.0)

Group 1=healthy, Group 2=mild impairment, Group 3=moderate impairment, Group 4=severe impairment

In addition to increasing concentrations of SPM 7605, renal impairment also led to increased exposure to metabolites SPM 5509 and SPM 7790 but no apparent effect on SPM 7789. The summary of PK parameters is listed in tables 33 to 35.

SPM 5509 plasma C_{max} was about 2-fold higher in subjects with severe renal impairment than in healthy subjects. Subjects with mild and moderate renal impairment had about 1.3-fold and 1.8-fold higher SPM 5509 plasma C_{max} than healthy subjects, respectively. Mean AUC increased by about 1.5-, 2.5-, and 3.4 for mild, moderate, and severe renal impairment, respectively. These increases in SPM 5509 exposure should not pose a significant safety risk based on the lower biding affinity of SPM 5509 to muscarinic receptors.

Table 33: PK parameters of SPM 5509 following 4 mg fesoterodine

Parameter	Unit	Geometric mean (CV%)			
		Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)
C_{max}	ng/mL	8.17 (32.8)	10.06 (42.1)	12.93 (29.5)	14.83 (33.0)
$C_{max,norm}$	ng/mL*kg	596.7 (36.8)	843.1 (46.4)	1042.3 (28.5)	1167.2 (36.1)
$AUC_{(0-tz)}$	ng/mL*h	111.59 (29.3)	170.61 (64.1)	280.08 (33.9)	376.21 (32.6)
$AUC_{(0-tz)norm}$	ng/mL*h*kg	8149.2 (26.9)	14302.8 (63.4)	22584.9 (36.5)	29616.5 (39.0)
$t_{½}$	h	6.43 (44.2)	7.49 (43.0)	11.23 (23.0)	13.78 (25.6)
t_{max} [1]	h	6 (3-8)	7 (6-10)	10 (6-10)	9 (6-10)
Ae_{ur}	µg	822.57 (33.8)	615.33 (61.0)	599.46 (23.6)	449.14 (18.5)
CL_{ren}	L/h	7.35 (22.1)	3.59 (86.9)	2.11 (43.4)	1.23 (27.8)
CL/f	L/h	35.07 (30.0)	22.68 (66.3)	13.33 (37.8)	9.58 (36.6)

Group 1=healthy, Group 2=mild impairment, Group 3=moderate impairment, Group 4=severe impairment
[1] median (range)

Table 34 shows the PK parameters of SPM 7789. C_{max} increased slightly with renal impairment severity while AUC decreased. These changes should not warrant a safety concern.

Table 34: PK parameters of SPM 7789 following 4 mg fesoterodine

Parameter	Unit	Geometric mean (CV%)			
		Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)
C_{max}	ng/mL	0.19 (17.8)	0.17 (36.6)	0.19 (47.0)	0.24 (57.2)
$C_{max,norm}$	ng/mL*kg	12.7 (29.0)	12.7 (41.2)	14.6 (34.8)	18.0 (42.2)
$AUC_{(0-tz)}$	ng/mL*h	1.05 (53.2)	0.52 (193.6)	0.80 (544.9)	0.79 (610.3)
$AUC_{(0-tz)norm}$	ng/mL*h*kg	69.7 (69.7)	39.9 (204.0)	60.8 (449.0)	58.9 (471.6)
t_{max} [1]	h	9 (4-48)	5.5 (3-48)	27 (4-48)	5.5 (5-48)
Ae_{ur}	mg	18.53 (97.3)	12.74 (83.0)	5.76 (32.7)	3.25 (102.2)
CL_{ren}	L/h	23.83 (22.2)	17.91 (105.7)	2.50 (32.2)	14.23 (370.7)
CL/f	L/h	1387.37 (32.3)	2866.16 (209.5)	3018.67 (1109.8)	2844.09 (1113.5)

Group 1=healthy, Group 2=mild impairment, Group 3=moderate impairment, Group 4=severe impairment
[1] median (range)

Table 35 shows the PK parameters of SPM 7790. The mean AUC and C_{max} increased by about 5.0- and 2.3-fold, respectively, in subjects with severe renal impairment relative to healthy controls. Mild and moderate renal impairment also increased exposure but to a lesser extent.

Table 35: PK parameters of SPM 7790 following 4 mg fesoterodine

Parameter	Unit	Geometric mean (CV%)			
		Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)
C_{max}	ng/mL	3.69 (45.7)	5.23 (52.9)	6.70 (46.1)	8.38 (35.8)
$C_{max,norm}$	ng/mL*kg	269.6 (31.6)	438.4 (59.0)	540.6 (34.2)	659.7 (27.1)
$AUC_{(0-tz)}$	ng/mL*h	54.71 (60.4)	115.82 (81.0)	194.24 (52.4)	275.15 (36.0)
$AUC_{(0-tz)norm}$	ng/mL*h*kg	3995.1 (43.5)	9709.2 (85.0)	15662.9 (43.3)	21660.7 (28.3)
$t_{½}$	h	7.61 (42.3)	8.58 (40.1)	14.85 (43.8)	10.21 (59.7)
t_{max}[1]	h	7 (3-8)	8 (5-15)	12 (10-30)	13.5 (8-24)
Ae_{ur}	µg	489.13 (40.6)	373.15 (32.4)	285.25 (83.8)	201.64 (46.5)
CL_{ren}	L/h	8.844 (37.7)	3.208 (92.7)	1.487 (75.5)	0.769 (53.0)
CL/f	L/h	69.67 (61.1)	32.26 (84.5)	17.32 (52.8)	12.25 (39.6)

Group 1=healthy, Group 2=mild impairment, Group 3=moderate impairment, Group 4=severe impairment
[1] median (range)

In conclusion the AUC of SPM 7605 increased by a factor of about 2.5 in subjects with severe renal impairment when compared to healthy subjects, the AUC of SPM 5509 increased by a factor of about 3.5, and the AUC of SPM 7790 increased by a factor of about 5.0. This reviewer concurs with the sponsor's proposal of limiting patients with severe renal impairment to doses no greater than 4 mg/day.

2.3.4 What is the effect of CYP2D6 polymorphism on fesoterodine PK?

Study SP565, described in Section 2.2.1, examined the pharmacokinetics of SPM7605 in CYP2D6 poor metabolizers (PM) and extensive metabolizers (EM). Information on the effect of CYP2D6 genotype on fesoterodine exposure was also available from additional PK studies where both CYP2D6 EM and PM subjects were enrolled. A summary of effects of CYP2D6 PM, presented as PM:EM ratios for AUC and C_{max}, are listed in table 36. Note: since CYP2D6 PM subjects lack CYP2D6 activity, these data should also represent drug interaction with strong CYP2D6 inhibitors.

The CYP2D6 poor metabolizer status (EM and PM) in the primary PK study SP 565 was determined by genotyping CYP2D6 variant alleles *3, *4, *5, and *6. In some subjects *7 and *8 variants were also tested (3 out of 16 EMs were in this latter group). If a subject has 2 variant alleles, then the subject would be classified as PM; all others are classified as EM. Since *7 and *8 were not tested in all subjects, there is a small probability that a subject with *7 or *8 variant be misclassified as EM. If this occurs, one would expect exposure to be increased compared to a group of all true EMs and lead to a lower observed effect due to PM genotype. However, an examination of study SP686 (QT study), where all EM subjects were screened for *3 - *8, showed that C_{max} and AUC were slightly higher in study SP 686 compared to SP 565. This suggests that EM subjects in the primary PK study SP 565 were all classified correctly.

CYP2D6 PMs have values for AUC and C_{max} that are about 2-fold higher than CYP2D6 EMs. CYP2D6 PMs were enrolled in phase 3 trial SP 584 and at the doses administered (4 and 8 mg/day) did not exhibit an increased heart rate compared to EMs. This observation is contrary to that observed in the QT study SP686, where increasing dose led to increased heart rate. It is possible that there is a small difference that was not detected in the phase 3 trial SP 584 due to

variability of a mixed patient population and the small number of PM patients (n=21-28). Common side effects (e.g., dry mouth) were higher in the 8 mg group compared to 4 mg but both doses were determined to be safe (see Medical Officer's review). No dose adjustment is recommended in CYP2D6 metabolizers. However, a combination of CYP2D6 PM/inhibition and CYP3A4 inhibition, may results in substantial exposure to SPM 7605 that warrants precaution and dose limitation (please see section 2.4.2 Effect of CYP3A4 Inhibition for further discussion and recommendations).

Table 36: Effects of CYP2D6 PM presented as PM/EM ratios for AUC and Cmax

Study #	N for PM	N for EM	AUC PM/EM ratio	C_{max} PM/EM ratio
SP 564	6	12	2.23	2.23
SP 565[a]	8	16	1.96	1.73
SP 683[b]	4	8	1.41	1.31
SP 684	6	11	2.31	2.13

[a] SP 565 is the primary PK study.
[b] The small increase in SP 683 may be due to its small sample size as the result is inconsistent with the 3 other studies.

2.3.5 What is the effect of race on fesoterodine PK?

The effect of Caucasian or Black African race on fesoterodine PK was examined in study SP649. Healthy young male volunteers of Caucasian or Black African (n=16 per group) were given single dose of 8 mg fesoterodine (2 x 4 mg ER tablets) or placebo (12 treated and 4 placebo per group). An Asian cohort was also planned but aborted due to recruitment problem (Study sites were in south Africa and the UK). *The result showed that pharmacokinetics of fesoterodine is similar between Caucasians and Black Africans* (See table 37 and figure 16 below).

The mean plasma SPM 7605 concentration vs. time profiles were similar between the two racial groups (figure 16). Black African:Caucasian ratios of mean AUC and C_{max} were both 0.91, representing a slightly lower exposure in the African population. On the other hand, exposure to metabolites SPM 5509 and SPM 7790 were slightly higher in Black African population (table 37). Concentrations of SPM 7789 were close to the lower limit of quantitation for both groups. Profiles of available data suggest similarity between the two groups with respect to SPM 7789.

Figure 16: plasma concentrations profile of SPM 7605 after oral administration of 8 mg fesoterodine in Caucasian and Black African subjects.

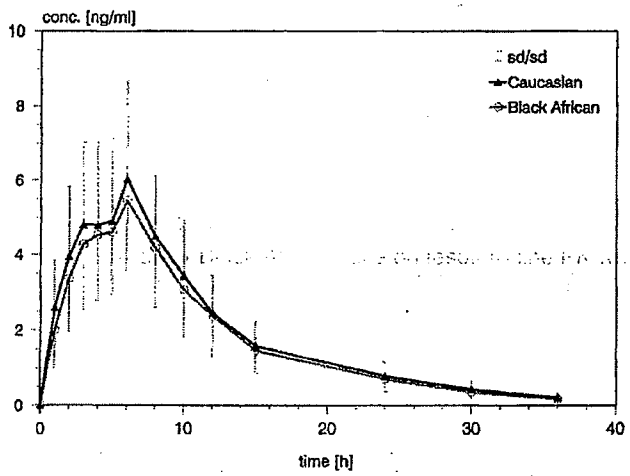


Table 37: PK parameters following single dose of 8 mg fesoterodine in Caucasians and Black Africans.

Parameter	dim	Caucasian mean	sd	n	Black African mean	sd	n
SPM 7605							
AUC(0-t_z)	[ng/ml*h]	70.74	27.45	12	64.13	22.81	12
AUC(0-∞)	[ng/ml*h]	72.99	27.80	12	65.83	23.17	12
C_{max}	[ng/ml]	6.05	2.68	12	5.48	1.89	12
t_{max}	[h]	5.83	0.58	12	5.50	1.24	12
$t_{1/2}$	[h]	6.72	1.79	12	6.44	1.31	12
CL/f	[l/h]	124.64	46.11	12	137.89	51.83	12
SPM 5509							
AUC(0-t_z)	[ng/ml*h]	214.3	47.1	12	224.4	53.2	12
AUC(0-∞)	[ng/ml*h]	225.3	53.5	12	231.7	53.0	12
C_{max}	[ng/ml]	14.30	3.09	12	16.89	5.04	12
t_{max}	[h]	7.33	1.72	12	5.50	1.09	12
$t_{1/2}$	[h]	7.16	1.81	12	6.67	1.05	12
CL/f	[l/h]	37.87	11.07	12	36.14	7.81	12
SPM 7790							
AUC(0-t_z)	[ng/ml*h]	123.76	37.62	12	127.47	37.95	12
AUC(0-∞)	[ng/ml*h]	134.18	40.82	12	134.14	39.20	12
C_{max}	[ng/ml]	7.84	3.11	12	9.02	3.42	12
t_{max}	[h]	6.58	1.62	12	5.75	1.54	12
$t_{1/2}$	[h]	8.77	2.15	12	7.87	0.95	12
CL/f	[l/h]	65.49	22.19	12	64.34	17.86	12

Renal clearance generally was also similar between the 2 ethnic groups (table 38).

Table 38: Descriptive statistics of parameters to characterize the renal excretion

Parameter	dim	Caucasian mean	sd	n	Black African mean	sd	n
Cl_{ren} SPM 7605	[l/h]	14.00	2.67	12	14.07	3.68	12
A_e SPM 7605	[µg]	956.46	323.23	12	841.25	180.08	12
A_e SPM 7605	[%]	18.5	6.2	12	16.3	3.5	12
Cl_{ren} SPM 5509	[l/h]	10.22	3.72	12	9.15	1.64	12
A_e SPM 5509	[µg]	2098.54	509.25	12	2010.26	388.02	12
A_e SPM 5509	[%]	35.3	8.6	12	33.8	6.5	12
Cl_{ren} SPM 7789	[l/h]	69.71	58.42	12	52.84	28.19	11
A_e SPM 7789	[µg]	112.99	65.62	12	105.70	54.98	12
A_e SPM 7789	[%]	2.1	1.2	12	1.9	1.0	12
Cl_{ren} SPM 7790	[l/h]	11.09	3.62	11	12.97	2.80	12
A_e SPM 7790	[µg]	1289.98	339.93	12	1614.52	468.81	12
A_e SPM 7790	[%]	24.3	6.4	12	30.4	8.8	12

In conclusion, there was no significant pharmacokinetic difference between Caucasian and Black African following 8 mg of fesoterodine.

2.4 Extrinsic Factors

2.4.1 What is the effect of concomitant food intake on fesoterodine PK?

The effect of food on fesoterodine PK was examined in study SP687. This was a randomized, open-label, 2-fold crossover trial with a single oral dose administration of 8mg fesoterodine to 16 healthy male subjects either in the fasted state or after a high-fat and high-calorie meal. Each of the periods consisted of 2 in-house days; both periods were separated by a wash-out phase of at least 1 week.

Figure 17 shows the SPM 7605 plasma concentration after dosing in both fasted and fed states. Table 39 shows the PK parameters. There were large variability in the primary PK parameters AUC(0-tz) and C_{max} (CV = 49 – 63%). On average, the values of both primary PK parameters AUC(0-tz) and Cmax were about 19% higher after fesoterodine administration in the fed state as compared to the fasted state. The corresponding 90% CIs for the ratio "fed"/"fasted" were calculated as (104%, 137%) for AUC(0-tz) and (94%, 149%) for Cmax. These CIs are outside the no-effect range of 80 - 125%.

Bioavailability of SPM 7605 expressed as $AUC_{0-\infty}$ was on average 12% higher for fesoterodine administration in the fed state compared to the fasted state (Note: subject 80014 was excluded due to apparent long $t_{1/2}$ leading to the extrapolated area of 52.5% of total AUC. The model adjusted mean was 40.81 which differ than the raw geometric mean of 44.63 given in the table). The corresponding 90% CI of the ratio "fed"/"fasted" was (97%, 129%) and thus was also not included in the acceptance range of (80%, 125%). The time to reach C_{max} was comparable for both conditions.

Figure 17: geometric mean time curves of SPM 7605 plasma concentration following 8 mg fesoterodine in fed or fasted state (n=16) (SP687)

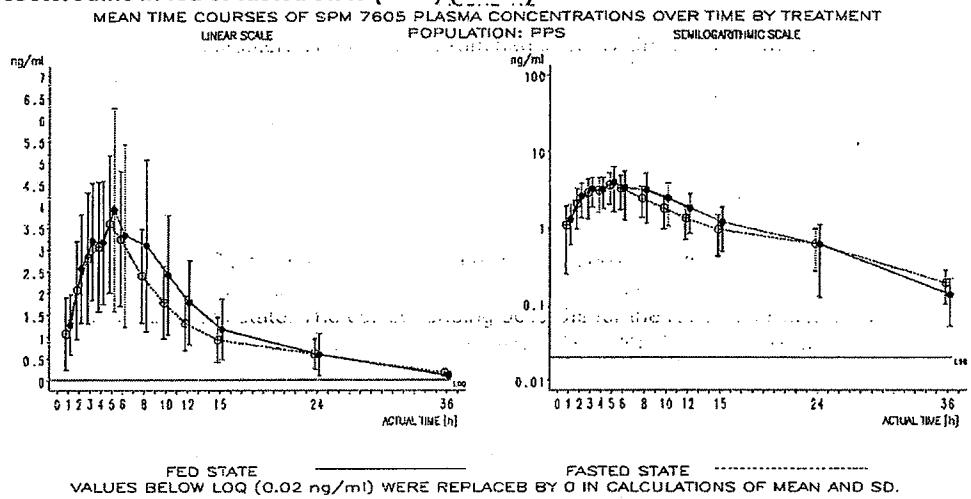


Table 39: PK parameters following 8 mg fesoterodine in fed or fasted state in healthy male volunteers (SP687)

Parameter (Unit)	Fesoterodine 8mg in fasted state Geometric Mean / CV (Range) N=16	Fesoterodine 8mg in fed state Geometric Mean / CV (Range) N=16
AUC(0-t_z) (h*ng/mL)	37.20 / 63.5% (7.46-73.24)	44.35 / 50.8% (11.95-96.79)
C_{max} (ng/mL)	3.30 / 62.3% (0.72-6.87)	3.92 / 49.28% (1.78-9.31)
AUC(0-∞) (h*ng/mL)	44.63 / 39.3%[a] (22.33-78.66)	45.75 / 50.4% (12.36-99.35)
CL/f (L/h)	0.18 / 39.3%[a] (0.10-0.36)	0.18 / 50.4% (0.08-0.65)
MRT (h)	13.69 / 24.67%[a] (9.53-23.14)	11.16 / 20.2% (7.25-16.36)
$t_{1/2}$ (h)	8.41[b] (5.32-33.60)	6.87[b] (3.88-11.44)
t_{max} (h)	5.0[c] (4.0-6.0)	4.5[c] (2.0-8.0)
λ_z (1/h)	0.082[c] (0.02-0.13)	0.101[c] (0.06-0.18)

[a] based on N=15 subjects since AUC(0-∞) was not valid for Subject 80014

[b] The median is shown for $t_{1/2}$ because the mean value for the fasted state was influenced by a very high estimated $t_{1/2}$ for Subject 80014 of 33.6 hours.

[c] median

In conclusion study SP687 showed that food increased exposure by about 19%. This is consistent with the 18% increase in AUC and 30% increase in C_{max} observed in study SP565 (see section 2.2.1.3). These small increases are not clinically significant and no dose adjustments are recommended. The similar changes in these 2 studies also support the robustness of formulations B (used in study SP 565) and D (used in study SP 687).

2.4.2 What is the effect of CYP3A4 inhibition on fesoterodine PK?

The effect of CYP3A4 inhibition was examined in 2 studies using ketoconazole 200 mg once daily (SP564) or twice daily (SP684). Each study included 18 healthy male subjects (12 extensive and 6 poor metabolizers for CYP2D6. For "fesoterodine + ketoconazole" treatment period, ketoconazole was given for 6 days with a single dose of 8 mg fesoterodine given on the fifth day. The "fesoterodine" treatment period included only a single dose of 8 mg fesoterodine. The studies were not blinded and no placebo was given. Note: the focus of discussion will be on the BID study SP684 with supporting data from the QD study SP564.

The PK data indicate an increase of exposure to SPM 7605 during co-administration of ketoconazole caused by CYP3A4 inhibition (figure 18 and tables 41 and 41a). Plasma concentrations were markedly increased when ketoconazole was co-administered with fesoterodine in both subgroups of poor and extensive metabolizers. Exposure to SPM 7605 expressed as AUC(0-tz) and C_{max} was approximately twice as high after the combined treatment of fesoterodine and ketoconazole compared to the treatment with fesoterodine alone (table 40). This result was observed in both poor and extensive metabolizers. The largest effect of ketoconazole 200 mg BID was observed in CYP2D6 PM subjects, where AUC(0-tz) and C_{max}

increased 2.5- and 2.1-fold, respectively. Terminal half-life of SPM 7605 was not significantly affected by co-administration of ketoconazole (about 7 hours after treatment with fesoterodine and 8 hours after co-administration of ketoconazole) and was comparable between poor and extensive metabolizers. Median T_{max} was 5 and 6 hours for both treatments and was comparable between poor and extensive metabolizers.

CYP3A4 inhibition alone may not warrant a dose adjustment. However, because SPM 7605 is metabolized mainly by CYP2D6 and CYP3A4, the blockade of CYP3A4 by ketoconazole in CYP2D6 PM resulted in significant increase in SPM 7605 exposure. Following administration of 8 mg fesoterodine to CYP2D6 PM taking ketoconazole 200 mg twice daily mean AUC(0-tz) was 217.16 ng/mL*hr (geometric mean, 31.9% CV) and C_{max} was 13.36 ng/mL (geometric mean, 27.9% CV) representing increases of 5.69- and 4.48-fold compared to CYP2D6 EM with no concomitant CYP3A4 inhibition. Increased adverse effects, particularly heart rate, are a potential concern with these elevated exposure levels. These levels are less than (but still very high compared to) those achieved in the thorough QT study for the supratherapeutic dose of 28 mg/day (SP 686: mean AUC = 242.5 ng/mL*hr and C_{max} = 20.7 ng/mL), where significant sustained elevation of heart rate was observed. Additionally, a real potential exits for a CYP2D6 PM (about 7 – 10 % of Caucasian population) to be given a drug that inhibits CYP3A4. The resulting exposure may lead to substantial increase in heart rate and precaution is needed when prescribing a CYP3A4 inhibitor and fesoterodine if the patient CYP2D6 status is PM or not known. Even though CYP2D6 EMs would not be at the same safety risk, separation by CYP2D6 status is still difficult due to high cost of genotype testing. Therefore, this reviewer recommends that the fesoterodine dose be restricted to no more than 4 mg/day when given to a patient taking a strong CYP3A4 inhibitor. There should not be a lack of efficacy since a strong CYP3A4 inhibitor should cause a doubling of exposure.

Figure 18: Plasma concentration of SPM 7605 (arithmetic mean)

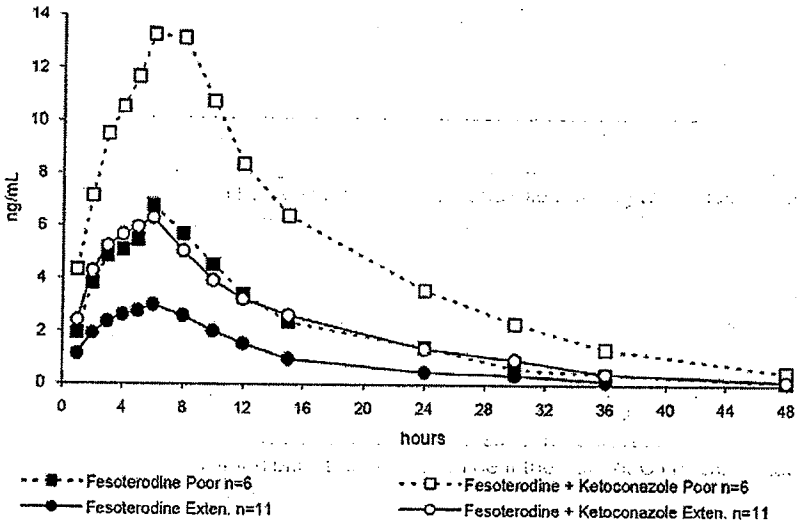


Table 40: Relative change in SPM 7605 exposure due to Ketoconazole

		Ketoconazole 200 mg QD		Ketoconazole 200 mg BID	
Variable	CYP2D6 status	Comparison (F+K)/(F) estimate	90% CI	Comparison (F+K)/(F) estimate	90% CI
AUC(0-tz) (ng/mL*h)	Poor	1.89	1.63-2.19	2.46	2.00-3.03
	Extensive	2.15	1.94-2.39	2.33	1.99-2.72
C_{max} (ng/mL)	Poor	1.51	1.22-1.87	2.10	1.56-2.83
	Extensive	2.20	1.90-2.56	2.02	1.62-2.52

Table 41: PK parameter of SPM 7605 (geometric mean) in CYP2D6 EM and PM in the present or absent of ketoconazole 200 mg twice daily.

Parameter	Extensive metabolizers (n=11)		Poor metabolizers (n=6)	
	feso	feso + keto	feso	feso + keto
$AUC_{(0\text{-}tz)}$ (ng/mL*h)	38.18 (39.3%)	88.28 (40.1%)	88.27 (35.3%)	217.16 (31.9%)
C_{max} (ng/mL)	2.98 (50.2%)	6.01 (44.4%)	6.36 (51.1%)	13.36 (27.9%)
$AUC_{(0\text{-}\infty)}$ (ng/mL)	39.01 (38.5%)	89.95 (39.6%)	89.50 (35.6%)	224.16 (32.7%)
Ae_{ur} (µg)	568.00 (25.1%)	760.51 (36.9%)	1263.18 (36.2%)	1373.63 (32.3%)
CL/f (L/h)	205.09 (38.5%)	88.94 (39.6%)	89.39 (35.6%)	35.69 (32.7%)
CL_R (L/h)	14.78 (23.9%)	8.60 (29.5%)	14.29 (38.1%)	6.33 (42.0%)
MRT (h)	12.60 (11.9%)	13.72 (15.2%)	13.06 (15.7%)	15.41 (20.2%)
$t_{1/2}$ (h)	6.95 (17.4%)	7.68 (21.2%)	6.98 (22.3%)	8.42 (31.9%)
t_{max} (h)*	6.0 (3.0-8.0)	5.0 (3.0-8.0)	6.0 (4.0-6.0)	6.0 (6.0-8.0)

* median (range)

Table 41a: PK parameter of SPM 7605 (geometric mean) in CYP2D6 EM and PM in the present or absent of ketoconazole 200 mg once daily.

Parameter	Extensive metabolizers (n=12)		Poor metabolizers (n=6)	
	Feso	Feso + keto	Feso	Feso + keto
AUC0-tz (ng/ml*h)	55.54	119.54	123.65	233.41
C_{max} (ng/ml)	4.32	9.52	9.62	14.53

Effect of ketoconazole on the exposure to metabolites beyond SPM 7605:

CYP3A4 inhibition also increased exposure to SPM 5509 but decreased exposure to SPM 7789 and SPM 7790.

On average the bioavailability of SPM 5509 expressed as AUC(0-tz) and Cmax was higher after co-administration of fesoterodine and ketoconazole than after administration of fesoterodine alone in both poor and extensive metabolizers. Mean AUC increased by 1.6 and 2.0-fold in CYP2D6 EM and PM, respectively. C_{max} increase was slightly less at 1.3 and 1.7-fold for CYP2D6 EM and PM, respectively. Since the potency of SPM 5509 is much lower than SPM 7605, these PK changes may not result in clinically significant changes.

The bioavailability of SPM 7790 expressed as AUC(0-tz) and Cmax was lower after co-administration of fesoterodine and ketoconazole than after administration of fesoterodine alone in both poor and extensive metabolizers.

In most subjects SPM 7789 plasma concentrations were below the limit of quantification after the combined treatment with fesoterodine and ketoconazole.

Table 42: PK parameters for SPM 5509. Ketoconazole increases exposure to SPM 5509.

Parameter	Extensive metabolizers (n=11) geometric mean (CV)		Poor metabolizers (n=6) geometric mean (CV)	
	feso	feso + keto	feso	feso + keto
$AUC_{(0-tz)}$ (ng/mL)	218.95 (24.3%)	347.79 (20.7%)	134.86 (53.1%)	262.35 (37.2%)
C_{max} (ng/mL)	13.75 (24.9%)	17.47 (24.6%)	7.54 (60.6%)	12.77 (43.5%)
CL/f (L/h)	36.06 (24.6%)	22.40 (20.2%)	58.34 (52.6%)	28.85 (36.3%)
$t_{1/2}$ (h)	7.02 (15.5%)	8.75 (18.8%)	7.72 (18.6%)	9.96 (33.5%)
t_{max} (h)*	6.0 (4.0-12.0)	6.0 (4.0-10.0)	6.0 (4.0-10.0)	9.0 (6.0-10.0)

* median (range)

In conclusion inhibition of CYP3A4 by ketoconazole increased SPM 7605 AUC by 2.3 – 2.5-fold and C_{max} by 2.0 – 2.1-fold (range represents change in EM and PM, respectively). The only other metabolite with increased exposure was SPM 5509 but is deemed not likely to cause clinically significant changes. The combination of CYP3A4 inhibition and CYP2D6 inhibition/poor metabolizers may result in high drug levels that could result in significant increase in heart rate and other adverse effects. Appropriate measures are needed to prevent doses higher than 4 mg/day from being given to this population.

2.4.3 What is the effect of CYP3A4 induction on fesoterodine PK?

The effect of CYP3A4 induction was examined using co-administration of 600 mg rifampicin once daily (SP 683). The study included 12 healthy male subjects (8 extensive and 4 poor metabolizers for CYP2D6). The trial consisted of 2 sequential treatment-periods:

Treatment "fesoterodine":
Day 1: Single oral administration of 8mg fesoterodine in the morning

Treatment "fesoterodine + rifampicin":
Days 3 - 8: Oral administration of 600mg rifampicin once daily in the evening
Day 9: Single oral administration of 8mg fesoterodine in the morning and oral administration of 600mg rifampicin in the evening
Day 10: Oral administration of 600mg rifampicin in the evening

Figure 19 shows the market decrease in concentrations of SPM 7605 when dosed together with rifampicin. Table 43 reports the PK parameters and table 44 shows the result of statistical analysis of the effect of CYP3A4 induction.

All measures of exposure showed that rifampicin significantly reduced bioavailability of SPM 7605. Bioavailability of SPM 7605 expressed as AUC(0-tz) was decreased by a factor of 4.3 and 4.5 during concomitant rifampicin treatment in extensive and poor metabolizers, respectively. Concomitant rifampicin treatment resulted in a decrease of C_{max} by a factor of 3.5 and 3.6 in extensive and poor metabolizers, respectively.

$AUC_{0-\infty}$ was 4.5 times higher after administration of fesoterodine alone compared to the combined fesoterodine and rifampicin treatment. Ae_{ur} was similarly about 4 times higher after administration of fesoterodine alone compared to co-administration of fesoterodine and rifampicin.

On the other hand, values for CL/f of SPM 7605 were about 4 times higher after co-administration of fesoterodine and rifampicin compared to fesoterodine alone. Values for CL_R, terminal half-life, and T_{max} were similar for both treatments.

Figure 19: Plasma SPM 7605 concentration following 8 mg fesoterodine in the present or absent of CYP3A4 induction by rifampicin (arithmetic mean) (SP683)

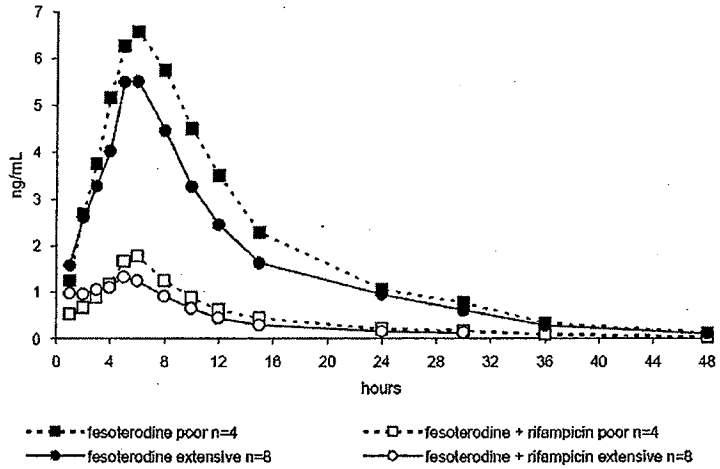


Table 43: PK parameters of SPM 7605 following 8 mg fesoterodine in the presence or absence of rifampicin

Parameter	Unit	Geometric mean (CV%)			
		Poor metabolizers (N=4)		Extensive metabolizers (N=8)	
		Fesoterodine	Fesoterodine + rifampicin	Fesoterodine	Fesoterodine + rifampicin
C_{max}	ng/ml	6.8 (24.4)	1.9 (19.2)	5.2 (64.7)	1.5 (61.3)
$AUC_{(0-tz)}$	ng/mL*h	87.8 (15.0)	19.6 (15.6)	62.4 (60.9)	14.4 (50.7)
$t_{½}$	h	7.4 (19.4)	8.4 (25.1)	7.5 (19.2)	7.0 (35.4)
t_{max}*	h	5.5 [5-6]	5.5 [5-6]	5.0 [5-6]	5.0 [1-6]
Ae_{ur}**	µg	1342.0±579.1	328.4±74.9	1054.1±425.6	256.7±99.6
CL_R	L/h	13.8 (64.6)	16.2 (40.9)	15.7 (23.0)	15.7 (18.4)
CL/f	L/h	89.5 (14.5)	392.8 (15.0)	125.6 (61.2)	526.7 (49.1)

Data source: Table 3.4.1 and Table 3.5.1

* Median [range]

** Arithmetic mean ± SD given for Ae_{ur}

Table 44: ANOVA comparison of SPM 7605 AUC and C_{max}

Variable	Metabolic status	Comparison (F+R)/(F) Estimate	
		Geometric mean [Range]	90% CI
$AUC_{(0-tz)}$ (ng/mL*h)	Poor	0.22 [0.17, 0.27]	0.17-0.29
	Extensive	0.23 [0.18, 0.32]	0.21-0.26
C_{max} (ng/mL)	Poor	0.28 [0.22, 0.38]	0.21-0.38
	Extensive	0.28 [0.17, 0.44]	0.23-0.35

Rifampicin treatment had a mixed effect on the metabolites beyond SPM 7605. Plasma concentration of SPM5509 decreased with rifampicin while concentrations of SPM 7789 and SPM 7790 increased. In the present of rifampicin, plasma SPM 7789 C_{max} increased by about 30% and 50% and AUC(0-tz) increased by 12% and 68% in CYP2D6 PM and EM, respectively. This small increase in SPM 7789, a minor metabolite, should not pose additional safety or efficacy risk. Plasma SPM 7790 C_{max} increased by 2.8 and 3.3 fold in CYP2D6 PM and EM, respectively, in the presence of rifampicin. Plasma SPM 7790 AUC(0-tz) increased by 2.3 and 2.6-fold in CYP2D6 PM and EM subjects, respectively, in the present of rifampicin. The highest mean AUC(0-tz) was observed in CYP2D6 EMs with rifampicin group, where the mean AUC was 312.5 (23.5% CV) ng/mL*hr. This increase in SPM 7790 level should not alter pharmacologic effect of fesoterodine since SPM 7790 does not appear to bind to muscarinic receptors. The toxicology of these AUC levels were tested in animals studies where the 312.5 ng/mL*hr AUC was covered in the mouse toxicity study with AUCs of 325 ng/ml*hr for male mice and 535 ng/mL*hr for female mice. Much higher exposure has been tested in dogs (up to 1272 ng/mL*hr).

The 3 tables below show PK parameters for the metabolites following 8 mg fesoterodine in the present or absent of rifampicin.

Table 45: PK parameters of SPM 5509

Parameter	Unit	Geometric mean (CV%)			
		Poor metabolizers (N=4)		Extensive metabolizers (N=8)	
		Fesoterodine	Fesoterodine + rifampicin	Fesoterodine	Fesoterodine + rifampicin
C_{max}	ng/mL	8.4 (25.4)	3.1 (22.0)	14.0 (30.7)	5.3 (46.6)
$AUC_{(0-tz)}$	ng/mL*h	137.7 (21.2)	39.2 (18.2)	213.5 (29.8)	61.6 (30.3)
$t_{1/2}$	h	8.0 (17.5)	8.5 (20.4)	8.0 (23.2)	6.8 (36.1)
t_{max}*	h	7.0 [5-8]	5.5 [4-6]	5.5 [5-8]	5.5 [1-8]
Ae_{ur}**	µg	1019.2±394.3	308.3±57.5	1760.8±535.2	517.0±198.5
CL_{ren}	L/h	6.9 (53.2)	7.6 (29.5)	7.9 (16.2)	7.7 (22.0)
CL/f	L/h	56.7 (21.1)	193.7 (15.8)	36.6 (29.3)	125.9 (28.9)

Data source: Table 3.4.2 and Table 3.5.2
* Median [range]
** Arithmetic mean ± SD given for Ae_{ur}

Table 46: PK parameters of SPM 7789

Parameter	Unit	Geometric mean (CV%)			
		Poor metabolizers (N=4)		Extensive metabolizers (N=8)	
		Fesoterodine	Fesoterodine + rifampicin	Fesoterodine	Fesoterodine + rifampicin
C_{max}	ng/mL	0.7 (20.4)	0.9 (13.1)	0.4 (51.2)	0.6 (70.3)
$AUC_{(0-tz)}$	ng/mL*h	9.1 (26.4)	10.2 (19.0)	3.1 (96.2)	5.2 (103.6)
$t_{½}$	h	9.7 (23.3)	8.3 (27.6)	9.7 (57.2)	8.2 (61.6)
t_{max}*	h	5.5 [5-8]	5.5 [5-6]	5.0 [3-6]	5.0 [1-8]
Ae_{tz}**	µg	145.4±49.7	165.6±24.4	69.9±31.4	113.1±56.1
CL_{ren}	L/h	14.6 (55.1)	15.4 (24.6)	17.9 (38.5)	15.8 (25.9)
CL/f	L/h	743.0 (21.6)	684.4 (19.2)	1426.8 (43.5)	1071.8 (77.1)

Data source: Table 3.4.2 and Table 3.5.3
* Median [range]
** Arithmetic mean ± SD given for Ae_{tz}

Table 47: PK parameters of SPM 7790

Parameter	Unit	Geometric mean (CV%)			
		Poor metabolizers (N=4)		Extensive metabolizers (N=8)	
		Fesoterodine	Fesoterodine + rifampicin	Fesoterodine	Fesoterodine + rifampicin
C_{max}	ng/mL	5.2 (7.9)	14.6 (17.1)	7.05 (33.7)	23.0 (39.5)
$AUC_{(0-tz)}$	ng/mL*h	102.3 (13.1)	230.9 (16.2)	118.6 (26.2)	312.5 (23.5)
$t_{½}$	h	10.6 (13.0)	10.1 (16.2)	8.9 (22.2)	8.0 (30.0)
t_{max}*	h	6.0 [5-10]	6.0 [5-10]	6.0 [5-8]	5.0 [2-8]
Ae_{tz}**	µg	790.6±283.0	1677.2±462.9	1091.8±287.2	2450.6±737.8
CL_{ren}	L/h	7.2 (48.4)	7.0 (34.0)	8.9 (16.7)	7.6 (17.5)
CL/f	L/h	73.8 (13.7)	32.8 (14.6)	64.9 (24.5)	24.9 (22.7)

Data source: Table 3.4.2 and Table 3.5.4
* Median [range] are given for t_{max}
** Arithmetic mean ± SD given for Ae_{tz}

In conclusion rifampicin administration may decrease exposure to SPM 7605 and potentially leads to a decrease in efficacy but should not pose a safety concern. The increase in exposure to SPM 7789 was small and also should not be a safety concern. The increase in SPM 7790 C_{max} and AUC were up to 3.3-fold and 2.6-fold, respectively, but should not alter the pharmacologic activity of fesoterodine sine this metabolite does not bind to muscarinic receptors. Furthermore, the absolute AUC was less than those tested in mice and dog toxicity studies. Therefore no dose adjustment is needed for safety, but efficacy may be reduced in the present of CYP3A4 inducers.

2.4.4 What is the effect of CYP2D6 inhibition on fesoterodine PK?

The effect of CYP2D6 inhibition could be ascertained from comparison of PK parameters from CYP2D6 extensive and poor metabolizers. Therefore, no drug interaction study using a CYP2D6 inhibitor was conducted. Please see section 2.3.4 for discussion and recommendations.

2.4.5 What is the effect of fesoterodine on hormonal contraceptives?

The effect of fesoterodine on the suppression of ovulation by oral hormonal contraception in healthy female subjects was examined in study SP677. This trial was a randomized, double-blind, placebo-controlled, 2-period crossover, multiple-dose trial with oral administration of 8mg fesoterodine extended-release (SPM 8272) once daily over 14 days (Days 1-14 of hormone cycle) in 30 healthy female subjects taking an oral hormonal contraceptive Minidril®(21-

day/cycle) containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) for at least 2 months prior to enrollment. Enrolled subjects were assigned to 2 cycles, starting with either fesoterodine or placebo.

The primary variable was the progesterone plasma levels on Days 19, 20, and 21 of each trial cycle. Additional pharmacodynamic variables included plasma levels of the ovarian steroid estradiol on Days 10, 13, 14, and 19-21 as well as of the pituitary gonadotrophins LH and FSH on Days 10, 13, and 14 as secondary variables.

The pharmacokinetic profile of the oral contraceptive on Day 13 also served as secondary variable including the following pharmacokinetic parameters: AUC(0-24), AUC(0-24)norm, C_{max}, Cmax,norm, and tmax of ethinylestradiol and levonorgestrel.

Concentrations of SPM 7605 (main metabolite of fesoterodine) in plasma were determined on Days 1 and 13.

Pharmacodynamic effects:

The results in table 48 shows that progesterone levels were clearly below 2 ng/mL suggesting that ovulation did not occur. On Day 21, the point estimate for the ratio of progesterone concentration in fesoterodine and placebo treated subjects was 1.54 but the mean was still a low 0.22 ng/ml for the fesoterodine group. Estradiol, LH, and FSH were sufficiently suppressed at all time points measured and in all subjects regardless of treatment with placebo or fesoterodine (table 49). There were many subjects with levels below limit of detection (BLD), which was replaced by the BLD value for statistical analysis.

Table 48: Plasma progesterone concentration

Treatment	Day	BLD[a]	n[c]	Progesterone Plasma Concentrations [ng/mL]			
				mean	SD	min	max
Fesoterodine	19	7	24[b]	0.18	0.16	0.05	0.72
	20	5	26	0.22	0.21	0.05	0.90
	21	3	26	0.22	0.18	0.05	0.78
Placebo	19	7	24[b]	0.28	0.31	0.05	1.34
	20	6	26	0.20	0.18	0.05	0.76
	21	7	26	0.14	0.14	0.05	0.63

Data source: Table 4.1.1.

a. Number of subjects with values below the limit of detection (BLD). These values were replaced by the BLD value of progesterone (0.05ng/mL) in the statistical analysis

b. No samples were available for two subjects as stated in Section 6.7

c. n=number of subjects

Table 49: Summary of estradiol, LH, and FSH plasma concentrations from all measurement days combined.

Hormone	Treatment	Values BLD [%]	mean	SD	min	max
Estradiol[a]	Fesoterodine	82.5	5.26	1.08	5	16.8
[pg/mL]	Placebo	81.2	5.18	0.49	5	7.46
LH[b]	Fesoterodine	62.8	0.71	1.06	0.15	5.1
[mIU/mL]	Placebo	56.4	0.89	1.18	0.15	4.92
FSH[c]	Fesoterodine	32.1	1.01	0.96	0.1	3.65
[mIU/mL]	Placebo	30.8	1.2	1.16	0.1	4.2

Pharmacokinetic effects:

Mean plasma concentrations versus time profiles of ethinylestradiol exhibited a similar pattern with or without fesoterodine. Moreover, inter-individual variability on plasma concentrations, as expressed by SD values, was comparable with both treatments. Examination of individual concentration profiles was consistent with the mean data. These data indicate that fesoterodine has no impact on the pharmacokinetics of ethinylestradiol. Table 50 below shows the summary of PK in terms of ethinylestradiol concentrations. The point estimates (and 90% CI) for ratio of fesoterodine/placebo AUC and C_{max} were 1.01 (0.96 – 1.07) and 1.03 (0.95 – 1.12), respectively. The data suggest fesoterodine did not significantly alter the PK of ethinylestradiol.

Table 50: plasma PK parameters for ethinylestradiol

Treatment		C_{max} [pg/mL]	t_{max} [h]	AUC(0-24) [pg·h/mL]
Contraceptive + Fesoterodine	mean (SD)	149 (55)	1.8 (0.8)	1298 (508)
	range	61-282	1-4	676-2443
Contraceptive + Placebo	mean (SD)	141 (40)	1.5 (0.5)	1280 (492)
	range	84-228	0.5-3	608-2381

Mean C_{max} plasma concentration of levonorgestrel was lower in the fesoterodine group (8.6 ± 2.9 pg/mg) compared to the placebo group (10.1 ± 4.9 pg/ml). Examination of individual profiles showed a similar pattern but levonorgestrel levels in fesoterodine period were generally less than or equal to those in the placebo period of same subject. The point estimate (and 90% CI) for ratio of treatment/placebo are: 0.87 (0.81 – 0.93) for C_{max} and 0.89 (0.85 – 0.94) for AUC(0-24). The ratios are less than 1 but 90% CI were within the 80 – 125% range, suggesting fesoterodine did not significantly alter the PK of levonorgestrel.

Concentration of SPM 7605 was measured at 4 hour post-dose on Day 1 and 13 and predose on Day 13. The mean concentrations at 4 hour post dose were similar between Day 1 and 13 suggesting no accumulation. However, the 4 hour time is close to T_{max} making this data not very useful for accumulation assessment or determination if fesoterodine's PK was affected by co-administration with the oral contraceptive.

In conclusion fesoterodine treatment did not appear to affect the PD markers progesterone, estradiol, LH, and FSH. Fesoterodine also did not significantly affect the plasma concentrations of ethinylestradiol and levonorgestrel as indicated by the 90% CIs that all fell within the normal limits of 80 – 125%.

2.4.6 What is the effect of fesoterodine on the PK of other drugs?

Effect of fesoterodine on enzyme inhibition and induction was examined in the following in vitro studies: BA 535-02, BA 472-02 (with amendment), 692, and 950. The results indicated that fesoterodine administration is not likely to induce the activity of CYP1A2, 2B6, 2C9, 2C19, and 3A4 (i.e., all tested isoforms) or inhibit the activity of CYP1A2, 2B6, 2C9, 2C19, 3A4, or 2D6 (i.e., all tested isoforms). CYP2C8 was not evaluated.

Study BA 535-02 examined the induction potential of SPM 8272 (i.e., fesoterodine) on CYP3A4 in cryopreserved human hepatocytes. Human hepatocytes from 3 donors were incubated for 72 hours with 9.5 nM (5 ng/ml) and 95 nM (50 ng/ml) of SPM 8272. Positive controls (dexamethasone 50 uM (Dex), rifampicin 20 uM (Rif)) and vehicle controls (DMSO 1%, acetonitrile 1%) were included. Activity was measured in the supernatant of the metabolism of testosterone into 6beta-hydroxytestosterone. mRNA levels were also measured but not considered due to large variability.

Table 51 shows the induction ratios relative to vehicle control. Using a cut-off ratio of 1.5 for presence of induction, rifampicin induced CYP3A4 in all livers in both vehicles whereas dexamethasone only induced CYP3A4 in 2 liver samples and only when acetonitrile was used as the solvent. Since DMSO can induce CYP3A4 activity (table 51), the assay was less sensitive in sequence 1 where DMSO was used as the solvent.

SPM8272 9.5 nM did not induce CYP3A4 in this assay. This concentration approximates the plasma C_{max} of SPM7605 following 8 mg fesoterodine in CYP2D6 EMs. At the 10-fold higher concentration of 95 nM, SPM 8272 induced CYP3A4 activity in the same liver that was induced by dexamethasone but to a slightly less extent (2.7 fold vs. 3.2 fold). Since dexamethasone is a weak inducer of CYP3A4, the induction ability of SPM 8272 is likely low even at supratherapeutic concentration. In conclusion, study BA 535-02 showed that therapeutic concentration of SPM 8272 does not induce CYP3A4 in hepatocyte in vitro.

Table 51: CYP3A4 induction factor (calculated by a ratio of 6beta-hydroxytestosterone in treatment:vehicle control)

Sequence	Donor/ Lot#	Induction Factor				
		Compound				
		SC	Dex	Rif	SPM8272 (9.5 nM)	SPM8272 (95 nM)
1	059	1.0	1.2	3.2	1.0	0.8
	082	1.0	1.3	1.8	0.8	1.2
	130	1.0	1.4	3.4	0.9	0.9
2	059	1.0	1.2	4.3	1.0	1.3
	082	1.0	1.7	2.5	1.1	1.0
	130	1.0	3.2	13.5	1.4	2.7

SC: solvent control, sequence 1: 1% DMSO, sequence 2: 1% Acetonitrile

Table 52: CYP3A4 activity (testosterone 6beta-hydrolase activity) as measured by concentration of 6beta-hydroxytestosterone (6β-OHT)

Donor/ Lot#	Compound	Sequence 1		Sequence 2	
		6β-OHT conc. [µM]	mean [µM]	6β-OHT conc. [µM]	mean [µM]
059	SC	12.8	12.1	3.7	3.6
		11.3		3.5	
	Dex	15.3	14.7	4.5	4.2
		14.1		3.8	
	Rif	40.5	39.3	20.8	15.3
		38.0		9.8	
	SPM8272 (9.5 nM)	11.9	12.3	3.7	3.7
		12.7		3.7	
	SPM8272 (95 nM)	7.6	9.4	4.7	4.8
		11.1		4.9	
082	SC	38.6	41.6	36.3	33.8
		44.5		31.3	
	Dex	54.4	52.5	60.9	59.0
		50.6		57.0	
	Rif	76.4	75.2	86.1	85.7
		73.9		85.3	
	SPM8272 (9.5 nM)	42.3	35.3	38.1	36.9
		28.3		35.6	
	SPM8272 (95 nM)	49.3	48.0	36.6	32.3
		46.6		27.9	
130	SC	23.7	23.4	8.4	7.4
		23.1		6.3	
	Dex	29.5	33.3	15.6	23.6
		37.0		31.5	
	Rif	79.0	78.5	94.7	100.1
		77.9		105.4	
	SPM8272 (9.5 nM)	15.9	20.0	9.8	10.6
		24.1		11.4	
	SPM8272 (95 nM)	24.4	21.5	20.4	19.9
		18.6		19.3	

SC: solvent control, sequence 1: 1% DMSO, sequence 2: 1% Acetonitrile

Study 692 examined the induction potential of fesoterodine on CYP3A4 as well as CYP1A2, 2B6, 2C9, and 2C19. hepatocytes were incubated with fesoterodine (20 and 200 nM), control inducers, or solvent control (water or acetonitrile) for 72 hours and CYP activities were assess in the supernatant using isoform specific probes. Each probe was examined in hepatocytes from 2 donors, examined in triplicates. Assay variability (among the triplicates) was generally less than 15%.

Table 53 shows a summary of results indicating that 20 and 200 nM fesoterodine did not have significant induction of the CYP enzymes tested. The positive controls showed that the enzyme activity was inducible in this system.

Table 53: CYP enzyme induction activity in cryopreserved hepatocytes

	Donor	Substrate (concentration)	Control inducer		Fesoterodine % of control	
			Compound (concentration)	% of control	20 nM	200 nM
CYP1A2	417	7-ethoxyresorufin	Omeprazole	462	102	117
		(5 µM)	(50 µM)	826	98.6	103
CYP2B6	417	(S)-mephenytoin	Phenobarbital	604	121	129
		(100 µM)	(200 µM)	610	117	84.8
CYP2C9	417	(S)-warfarin	Rifampicin	435	103	97.6
		(10 µM)	(20 µM)	359	109	102
CYP2C19	417	(S)-mephenytoin	Rifampicin	595	114	119
		(100 µM)	(20 µM)	n.t.	n.t.	n.t.
CYP3A4	417	Testosterone	Rifampicin	1276	131	124
	421	(250 µM)	(20 µM)	372	116	79.8

n.t. no metabolic turnover

b(4)

The inhibition potential of fesoterodine on CYP3A4, 2D6, 1A2, 2C9, and 2C19 activity was examined in study BA 472-02 and its one amendment. This was a competitive endpoint assay using specific CYP-substrates in the presence of test compounds or specific control inhibitor. Appropriate controls (zero incubation time, no test compound, or no inhibitor) were also evaluated. The system uses cDNA expressed microsomes of each specific CYP enzymes tested [redacted]). The compound SPM 6923 was used to represent SPM 7790.

b(4)

The results were fitted to calculate log IC_{50}. IC_{50} were obtained by taking the antilog. Ki values were calculated based on published Km using the same enzyme system. Table 54 shows the IC_{50}, Ki, and I/IC_{50} ratios for each CYP and tested drug/metabolite. The concentration used for [I] are mean C_{max} from 8 mg fesoterodine given to healthy CYP2D6 EM as follow: SPM 8272 = none, SPM 7605 = 3.98 ng/mL (11.7 nM), SPM 5509 = 14.8 ng/mL (37.8 nM), and SPM 7790 = 7.47 ng/mL (21.4 nM).

Fesoterodine and its metabolites SPM 7605, SPM 5509, and SPM 7789 could inhibit CYP3A4 and CYP2D6 at very high concentration that is at least about 500 fold higher than observed therapeutic concentrations based on I/Ki ratios. CYP2C9 inhibition was minimal and no inhibition of CYP1A2 and CYP2C19 were observed at up to 200 uM. The minor metabolite SPM 7789 was not tested the potential is likely low due its lower therapeutic concentration and structural similarity with the tested metabolites. Therefore, in conclusion there is minimal risk that fesoterodine administration would inhibit drug metabolism by CYP1A2, 2C9, 2C19, 3A4, or 2D6.

Table 54: enzyme inhibition potential of fesoterodine and its metabolites (study BA 472-02).

	Log IC_{50}	IC_{50}[uM]	Ki[uM]	I/Ki
CYP3A4				
SPM 8272	3.638±0.120	4.3	2.8	-
SPM 7605	4.685±0.071	48.5	30.9	< 0.001
SPM 5509	5.191±0.538	155.2	99.1	< 0.001
SPM 6923	NI			-
Ketoconazole[a]	1.273±0.046	0.019	0.012	
CYP2D6				
SPM 8272	4.193±0.043	15.6	7.8	-
SPM 7605	4.001±0.040	10	5	0.002
SPM 5509	4.342±0.062	22	10.9	0.003

SPM 6923	NI			-
Quinidine [a]	1.251±0.041	0.018	0.009	
CYP1A2				
SPM 8272	NI			-
SPM 7605	NI			-
SPM 5509	NI			-
SPM 6923	NI			-
Furafyline [a]	3.033±0.047	1.08	0.45	
CYP2C9				
SPM 8272	5.680±0.512	478.35	246.28	-
SPM 7605	LI			-
SPM 5509	5.464±0.211	291.32	149.99	< 0.001
SPM 6923	LI			-
Sulfaphenazole [a]	2.538±0.059	0.34	0.18	
CYP2C19				
SPM 8272	NI			-
SPM 7605	NI			-
SPM 5509	NI			-
SPM 6923	NI			-
Omeprazole [a]	3.457±0.037	2.87	1.55	
NI= no interaction, LI = low interaction and calculation of IC_{50} was not possible, [a] median of 3 runs				

Study 950 examined the effect on inhibiting CYP2B6. Table 57a shows the summary of results. Only SPM 8272 and SPM 7605 had inhibitory activity on CYP2B6 at concentrations up to 200 uM. The ratio of $[I]/IC_{50}$ for SPM 7605 is less than 1/1000 indicating little potential for in vivo inhibition at therapeutic level.

Table 57a: enzyme inhibition potential of fesoterodine and its metabolites (study 950).

	Log IC_{50}	IC_{50}[uM]	I/IC_{50}
CYP2B6			
SPM 8272	4.55±0.07	35.8	-
SPM 7605	4.83±0.18	68.3	< 0.001
SPM 5509	NI	NI	-
SPM 6923	NI	NI	-
TCP[a]	3.91±0.06	7.32	
[a] TCP = tranylcypromine, NI = no inhibition			

2.4.7 Is there a need to examine the potential for dose-dumping due to alcohol consumption?

The sponsor provided the following response:

> "The extended release formulation (drug product) does not disintegrate in vitro in ethanolic solutions although addition of ethanol to the dissolution medium in vitro or to the gastro-intestinal fluid in-vivo may increase the dissolution rate in comparison to the "non-ethanolic" solution.
>
> However, due to the technological properties of the extended release formulation [redacted] a rapid release of the active drug substance or 'dose dumping' by the addition of ethanol is not possible.....
>
> In a worst case scenario from a clinical perspective, intake of the extended release formulation of fesoterodine would lead to immediate release of fesoterodine from the formulation.

b(4)

In the first-into-man trial SP560, single oral doses up to 16 mg fesoterodine immediate release were administered to healthy male subjects. In general, fesoterodine was safe and well tolerated in this trial. Fesoterodine was rapidly absorbed and its active metabolite, SPM 7605, was eliminated with a half-life of about 4 hours.

Whilst maximum plasma concentrations were in a comparable range, exposure following administration of 16 mg fesoterodine immediate release in SP560 (AUC(0-tz): 108.14±35.75 ng*h/ml; Cmax: 23.42±8.29 ng/ml) (SP560 Table 12.2.4) was well below exposure following 28 mg fesoterodine sustained release in 64 male and female healthy subjects in SP686 (AUC(0-t,ss): 242.46±108.17 ng*h/ml; Cmax,ss: 20.73±8.28 ng/ml) (SP686 Table 15.3.1), which was safe in this trial.

The worst case scenario following accidental intake together with alcohol is described above and considered to be adequately covered. In conclusion, there are no plans to conduct an alcohol interaction study."

Additionally, the safety risk of dose-dumping due to alcohol should not accumulate after multiple dose-dumps due to the short $t_{1/2}$ (about 4 hours) of the drug following dosing of immediate release formulation. However, efficacy may be decreased at later time due to low drug levels.

Following discussion with the CMC reviewer to confirm the properties of the [redacted] and the Medical Officer to confirm the safety of the immediate release doses, this reviewer concurs with sponsor that a separate study to examine the effect of alcohol consumption is not warranted. b(4)

2.5 General Biopharmaceutics

Review notes:
Studies reviewed: SP681 compared 2x4mg formulation B and 1x8mg formulation D, SP877 evaluated dose proportionality between 1x4mg and 1x8 mg formulation F, SP565 evaluated dose proportionality between 1x4mg and 2x4 mg formulation B.

Studies not reviewed: SP842 (BE study of formulations E vs. F manufactured at different sites), SP685 (relative PK of formulations A, B, and C), and SP562 (PK of 2 tablets of formulation A). These studies were not reviewed since they would not provide any bridging information. The BE study SP 842 used a formulation F that was manufactured at a new site in USA. The sponsor does not plan to use that new site to produce the commercial drug product.

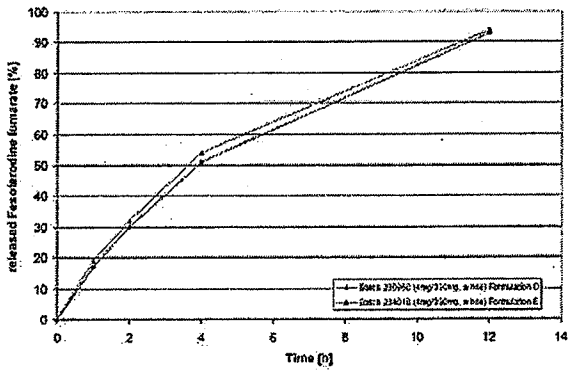
2.5.1 Is the to-be-marketed formulation identical to the one used for the phase 3 efficacy trials?

The phase 3 efficacy trials used drug product from formulations D and E. During the scale up of the manufacturing process of formulation D [redacted]

by the same amount, this resulted in formulation E [redacted] b(4)

[redacted] This was considered a level 1 change and in-vitro dissolution was used to compare the formulations. Figure 20 show similar dissolution profiles of 4 mg tablets of formulations D and E. Similar dissolution profiles were also observed with the 8 mg tablets, where the similarity F2 value was 83.7 indicating formulations D and E were similar.

Figure 20: Dissolution profiles of 4 mg formulation D and E in water



The to-be-marketed formulation, formulation F, included only a change in the film coat from formulation E. The coating was changed from white to light blue for the 4 mg ER tablet and blue for the 8 mg ER tablet. This minor change was bridged with in vitro dissolution studies. Figure 21 shows the similar dissolution profiles of 8 mg formulations E vs. F in phosphate buffer ph 6.8 (f2 = 81.5). Figure 22 shows comparative dissolution profiles of formulations B – F, including similar profiles for formulations E and F. These data indicate the change in film coat did not affect the release of fesoterodine.

Figure 21: Dissolution profiles of 8 mg formulations E and F in phosphate buffer pH 6.8

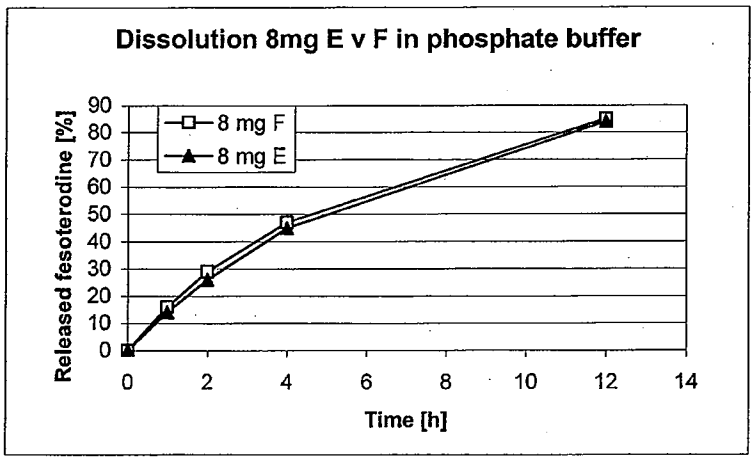
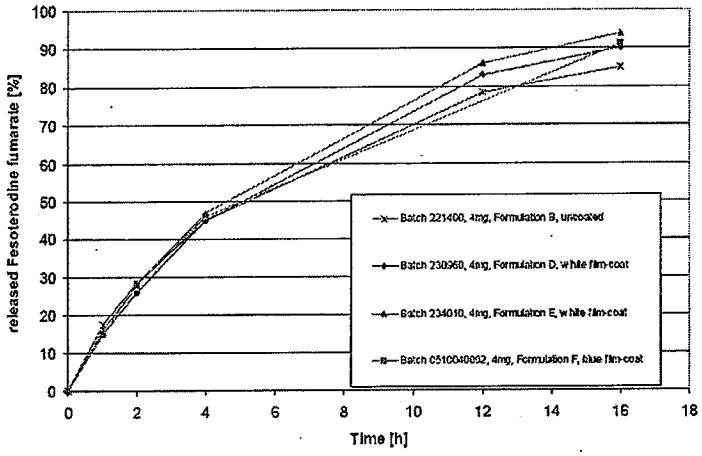
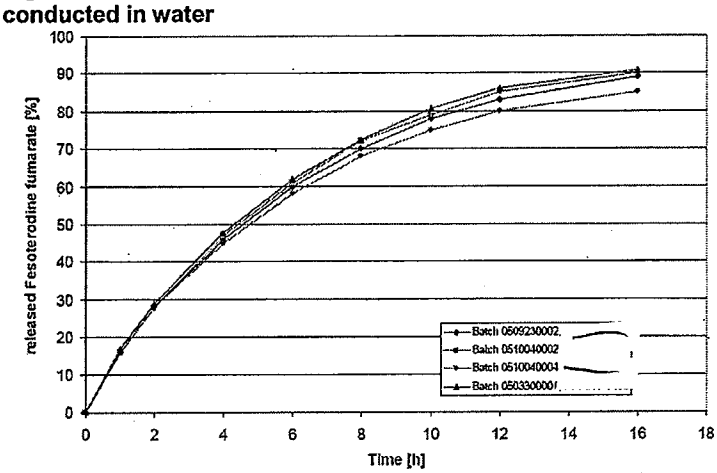


Figure 22: dissolution profile of 4 mg formulations B, D, E, and F in phosphate buffer pH 6.8



Additionally, within formulation F, there was a manufacturing change [redacted]. This was deemed a level 2 change by ONDQA and sponsor conducted in vitro dissolution studies in water, 0.1 N HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8 to determine similarity. Figure 23 show an example of dissolution profile comparison conducted in water. The dissolution profiles in all media were very similar and calculated F2 values were at least 68.2 in phosphate buffer, 67.5 in water, 70.9 in 0.1 N HCl, and 70.4 in acetate buffer. The individual mean values for each test point and [redacted] did not differ more than 6% from the mean values of the [redacted] material in all media. Therefore the formulation F tablets produced by [redacted] are similar to that produced by [redacted] method. b(4)

Figure 23: dissolution profiles of 4 mg formulation F [redacted] conducted in water



b(4)

Sponsor also conducted study SP877 examining the dose proportionality of 4 and 8 mg tablets of formulation F. The data suggested dose proportionality of the 2 tablet strengths. Since, fesoterodine was shown in study SP565 to be dose proportional using multiples of 4 mg tablets, the dose proportionality in SP877 suggests that 2 tablets of 4 mg strength could be substituted for 1 tablet of 8 mg strength formulation F.

In summary, there were minor changes in the formulation and manufacturing of the drug products used in phase 3 trials and the to-be-marketed product. These changes were considered level 1 or 2 changes and were bridged via in vitro dissolution tests. The results indicated that formulations D, E, and F were similar.

Additional note: Sponsor has indicated that the imprinting of the to-be-marketed formulation may change due to the merger with Pfizer. If this is done, in vitro dissolution bridging studies will need to be submitted. This issue is pending.

2.5.2 Were there any formulation changes prior to phase 3?

The only ER formulation that was used in supporting clinical studies prior to formulation D was formulation B. There were substantial formulation changes from B to D, including change in the core of the tablets. Bridging of formulations B and D can be assessed by a bioequivalence study (SP681) comparing 2 tablets of 4 mg formulation B and 1 tablet of 8 mg formulation D. Indirect bridging of 1 tablet of 4 mg formulation B and 1 tablet of 4 mg formulation D can be assess by examining dose proportionality within formulations B and F as were examined in studies SP565 and SP877, respectively. The following section will discuss the direct and indirect bridging in order.

The bioequivalence of 2x4 mg tablets of formulation B compared to 1x8 mg tablet of formulation D was examined in study SP681. This was a randomized, non-blind, 2-fold crossover trial with single oral dose administration of 8mg fesoterodine as one 8mg tablet (formulation D) in comparison with two 4mg tablets (formulation B) to 16 healthy male subjects. The pharmacokinetic profile of SPM 7605 (main metabolite of fesoterodine) was determined for each of the 2 formulations.

Figure 24 shows the plasma concentration profiles of SPM 7605. The profiles from the 2 treatments are very similar. Table 55 shows the calculated PK parameters for the 2 treatments.

Figure 24: Plasma SPM 7605 concentrations (geometric mean) of 2x4 mg B and 1x8 mg D

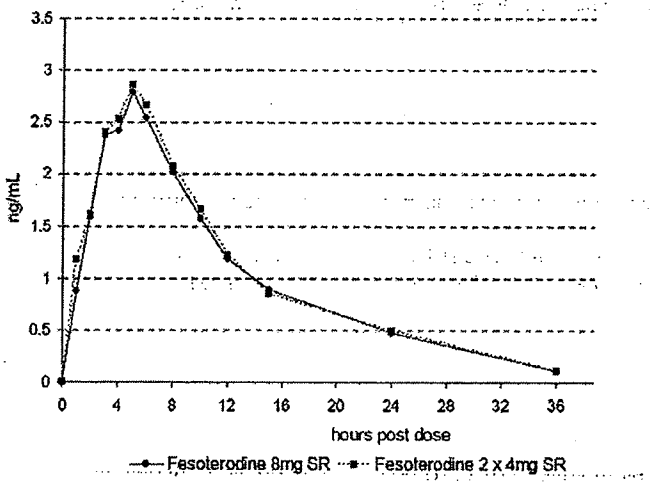


Table 55: PK parameters of SPM 7605 following 1x8 mg formulation D (A) and 2x4 mg formulation B (B).

Parameter [Unit]	(A) Fesoterodine 1 x 8mg SR Geometric Mean / CV (Range)	(B) Fesoterodine 2 x 4mg SR Geometric Mean / CV (Range)
$AUC_{(0-tz)}$ [h*ng/mL]	36.31 / 38.5% (20.16-78.92)	37.19 / 34.3% (22.34-62.87)
C_{max} [ng/ml]	3.01 / 44.2% (1.48-7.28)	3.06 / 39.5% (1.90-5.58)
$AUC_{(0-\infty)}$ [h*ng/mL]	38.47 / 36.4% (20.41-79.94)	39.08 / 32.4% (22.79-65.99)
CL/f [1/h]	208 / 36.4% (100-392)	205 / 32.4% (121-351)
MRT [h]	12.62 / 26.2% (9.33-21.66)	12.57 / 19.2% (8.83-17.93)
λ_z [1/h]	0.10 / 37.5% (0.05-0.19)	0.09 / 37.4% (0.05-0.17)
$t_{1/2}$ [h]	7.16 / 37.5% (3.64-13.15)	7.54 / 37.4% (4.16-14.96)
t_{max} [h]	5.0[a] (3.0-10)	5.0[a] (1.0-6.0)

[a] median

For the primary PK parameters AUC(0-tz) and Cmax, the calculated 90% CIs for the ratios "1 x 8mg fesoterodine D"/"2 x 4mg fesoterodine B" were 0.98 (0.89 – 1.07) and 0.99 (0.86 – 1.13), respectively. These CIs were completely included within the bioequivalence acceptance range of (80%, 125%).

For the secondary PK parameter AUC(0-inf), the 90% CI for the treatment ratio (0.98 [0.90 – 1.08]) was also completely included within the bioequivalence acceptance range. Statistical analysis of T_{max} did not indicate any difference between the 2 formulations.

The 2 formulations also showed very similar results with regard to all other secondary PK parameters, in particular concerning terminal half-life (t1/2) with mean values of 7.2 hours for 1 x 8mg fesoterodine D and 7.5 hours for 2 x 4mg fesoterodine B. This reassures the similarity of the two formulations as the apparent $t_{1/2}$ is partly influenced by the extended release nature of the formulation.

In addition to the in vivo BE trial, in vitro dissolution studies also showed similar dissolution profiles between formulations B and D (figure 22).

In conclusion, this trial demonstrated bioequivalence of 1 x 8mg fesoterodine formulation D and the 2 x 4mg formulation B after single-dose administration. In vitro dissolution data also support similarity between formulations B and D.

Indirect bridging:

The above BE study did not address the bridging of 1x4 mg formulation B vs. 1x4 mg formulation D. this information is useful for determining the PK of 4 mg dose of the to be marketed formulation. However, indirect bridging could be obtained from dose proportionality evaluation within formulation B and formulation F (equivalent to formulation D).

Study SP 565 showed dose proportionality between 1x4 mg and 2x4 mg formulation B with 4mg/8mg dose normalized mean (90% CI) ratios of 0.93 (0.87 – 0.99) for AUC(0-tz) and 0.92 (0.82 – 1.04) for C_{max}.

Study SP877, a 2-period crossover study in 24 healthy, young, males taking single dose of 1x4 mg or 1x8 mg fesoterodine formulation F tablets, showed that 1x4 mg and 1x8mg formulation F were dose proportional. The 4mg/8mg dose normalized mean (90% CI) ratios for AUC and C_{max} were 0.99 (0.91 – 1.09) ng/ml*h and 0.96 (0.86 – 1.07) ng/mL, respectively. A summary of PK parameters are listed in the table below.

Table 55a: SPM 7605 PK parameters from SP 877.

Parameter (unit)	4mg tablet	8mg tablet
$AUC_{(0-\infty)}$ (ng/mL*h)	21.118 (52.8%)	43.047 (45.6%)
$AUC_{(0-\infty),norm}$ (ng/mL*h/mg)	5.2794 (52.8%)	5.3808 (45.6%)
C_{max} (ng/mL)	1.943 (47.7%)	3.976 (43.2%)
$C_{max,norm}$ (ng/mL/mg)	0.48571 (47.7%)	0.49702 (43.2%)
$AUC_{(0-tz)}$ (ng/mL*h)	19.340 (55.1%)	41.077 (46.3%)
$AUC_{(0-tz),norm}$ (ng/mL*h/mg)	4.8350 (55.1%)	5.1346 (46.3%)
t_{max} (h)	5.0 (3-6)	5.0 (2-6)
$t_{1/2}$ (h)	7.1343 (43.7%)	6.4020 (41.4%)
MRT (h)	11.992 (31.8%)	11.420 (25.7%)
CL/f (L/h)	189.42 (52.8%)	185.84 (45.6%)

n= 24 subjects per treatment
a. implausible samples excluded (see Section 6.7)
Note: Results for t_{max} show median (range). All other parameters show geometric mean (coefficient of variation)

Since both formulations B and F (equivalent to D) were dose proportional and 2x4mg B was bioequivalent to 1x8 mg D, indirect BE bridging of 1x4 mg B and 1x4 mg D is completed. This approach does not meet the standard statistical requirements; however it does provide sufficient support for the review of phase 1 data in this NDA.

Conclusions: The direct and indirect bridging data suggest that formulation B is bioequivalent to formulation D and data from all clinical pharmacology studies using multiples of 4 mg formulation B tablets may be used to support this NDA.

2.5.3 Is the dissolution profile for the final formulation acceptable in term of dissolution rate specification?

Please see ONDQA review for dissolution rate specifications.

2.6 Analytical Section

2.6.1 What bioanalytical methods were used to assess concentrations?

SPM 7605 in human plasma was measured using a validated HPLC-electrospray MS/MS assay (validation report BA 394-03).

SPM 7605 in human urine was measured using a validated HPLC-electrospray MS/MS assay (validation report BA 413-02).

Plasma concentrations of SPM5509, SPM 7789, and SPM 7790 were measured using a validated HPLC-electrospray MS/MS assay (validation report BA 437-03 (for using an ——) and validation report BA 447-03 (for using an ——nass spec)). b(4)

Urine concentrations of SPM5509, SPM 7789, and SPM 7790 were measured using a validated HPLC-electrospray MS assay (validation report BA 448-03).

Plasma concentrations of all metabolites (i.e., SPM 7605, 5509, 7789, and 7790) were measured simultaneously using a validated HPLC-electrospray MS/MS assay (validation report BA 540-03).

Urine concentrations of all metabolites (i.e., SPM 7605, 5509, 7789, and 7790) were measured simultaneously using a validated HPLC-electrospray MS/MS assay (validation report BA 572-03).

2.6.2 Were the bioanalytical methods adequately validated?

All assays were validated as indicated in the referenced validation reports listed above in section 2.6.1. Validation parameters were acceptable.

3 Detailed Labeling Recommendations

In addition to the sponsor's proposal of limiting patients with severe renal impairment to the 4 mg/day dose, we recommend the same limitation be placed on patients taking a strong CYP3A4 inhibitor.

4 Appendices

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

Appendix 4.2.1:

SP686 – Thorough QT Study

Title of trial: 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 steady state to healthy male and female subjects: a thorough QT trial

Note:

- *This was a parallel design and not a crossover design. Therefore, individual placebo correction can not be done.*
- *The placebo and fesoterodine arms received 7 tablets per day and moxifloxacin arm received just 1 moxifloxacin tablet – effectively unblinding the moxifloxacin arm.*

Objectives: Primary objective of this trial was to define the electrocardiographic effects of fesoterodine at steady-state after administration of 4 or 28mg/day for 3 days. As secondary objectives the correlation between fesoterodine plasma concentrations and QTcF were examined, and the safety and tolerability of the treatment was evaluated.

Note:

- *Fesoterodine 28 mg/day plasma levels in this study (AUC0-tz = 242.5 ± 108.2 ng/ml*hr, C_{max} = 20.7± 8.3 ng/ml) cover a worst case scenario of fesoterodine dosing, e.g., a CYP2D6 poor metabolizer with concomitant CYP3A4 blockage (i.e., ketoconazole 400 mg/day) receiving 8 mg/day fesoterodine (AUC0-tz = 217.2 ± 69.3 ng/ml*hr, C_{max} = 13.4± 3.7 ng/ml (study SP 684)).*
- *Moxifloxacin was given for 3 days rather than the preferred single dose. However, QT interval after one dose of moxifloxacin (Day 1) is available.*

Methodology: This trial was a double-blind, single-site, randomized, placebo- and positive controlled, parallel-design trial with multiple oral dose administration of fesoterodine, moxifloxacin, or placebo. Healthy subjects had 3 days of treatment with 4mg/day or 28mg/day fesoterodine, 400mg/day moxifloxacin, or placebo. The electrocardiographic effects and pharmacokinetics were determined.

Number of subjects (planned and analyzed): The planned number of subjects was 256 (64 per treatment group). A total of 261 subjects were enrolled and randomized; 65, 64, 68, and 64 subjects in the placebo, fesoterodine 4mg/day, fesoterodine 28mg/day, and moxifloxacin treatment groups, respectively. One hundred thirty one subjects were analyzed for the primary pharmacokinetic (PK) variables and 261 subjects were analyzed for the primary pharmacodynamic variables.

Diagnosis and main criteria for inclusion: Subjects were included if they were a healthy male or female between 45 and 65 years of age. In addition, subjects were genotyped as extensive metabolizers for cytochrome P450 2D6. Subjects were excluded from the trial if they had a history or presence of urinary retention, obstructive disturbance of bladder emptying, micturition disturbance, nocturia or pollacisuria, e.g., prostatic hyperplasia, or urethral stricture. Male subjects were excluded if they had a history of benign prostate hyperplasia, had a residual urinary volume greater than 80mL (as measured by ultrasound), or a maximum urinary flow rate less than 15mL/s (as measured by uroflowmetry, an amount of at least 125mL has to be urinated) within 12 weeks prior to the first dose. All subjects who had a history of ischemic heart disease or a positive diagnostic cardiac stress test (eg, treadmill or bicycle ergometry) within 12 weeks prior to the first dose were excluded from the trial.

Test product, dose and mode of administration, batch number: Fesoterodine 4mg extended-release tablets containing 4mg fesoterodine fumarate (SCHWARZ BIOSCIENCES GmbH, Germany). Batch number was 234010.

Pharmacokinetics and pharmacodynamics:
The primary variable was the change from Baseline in QTc based on Fridericia correction method. Time-average, time-matched, and maximum time-matched change from baseline analyses were performed.

Secondary variables were the following:

Electrocardiograms:
• Change from Baseline in QTc based on individual and Bazett correction methods
• Change from Baseline in heart rate, PR interval, QRS interval, ECG morphological patterns, and uncorrected QT interval

Pharmacodynamics:
• Correlation between the QTcF, change in QTcF, and plasma concentration of SPM 7605
Pharmacokinetics:
• AUC0-tz,ss, AUC0-tz, ss, norm, Cmax, ss, Cmax, ss, norm, tmax,ss, and CL/f

Results:

1. Correction methods:

QTcF was the primary correction methods specified in this study. The results from this study of the 3 correction methods versus RR interval are shown in the next 3 figures. A spline fit of the data is indicated by the solid line in each plot. The table accompanying each figure lists the results of linear mixed effect modeling of the RR-QTc relationship. There is a clear negative correlation with the Bazett correction method. QTcF had the smallest slope. However, both QTcI and QTcF methods had similar, slightly positive correlation with increasing RR interval (i.e., decreasing heart rate). A positive slope may underestimate QT interval for patients with elevated heart rate. However, the slope is relatively small (a heart rate increase from 60 to 80 bpm (RR from 1000 to 750 mses) could lead to QTc underestimation of 4.9 msec) and either QTcF or QTcI could be used.

Figure 25: QTcB vs. RR interval

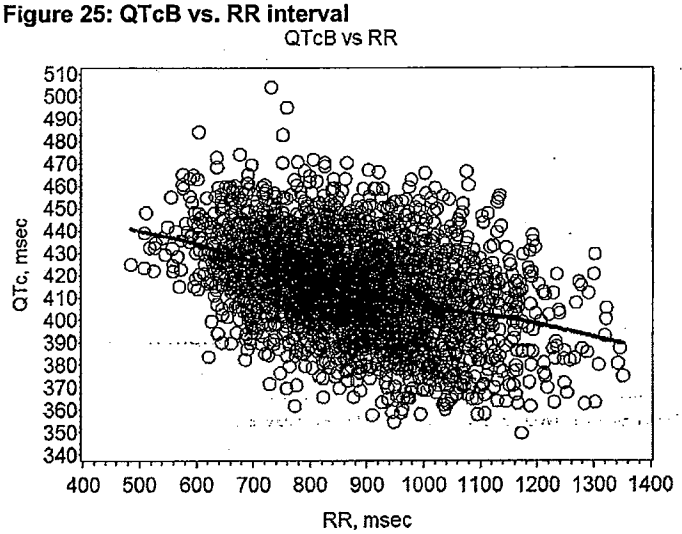


Table 56: QTcB-RR analysis results

Obs	Intercept	Effect	Estimate	StdErr	DF	tValue	Probt
1	467.99 ms	RR (ms)	-0.06114	0.00217	260	-28.16	<.0001

Figure 26: QTcI vs. RR interval

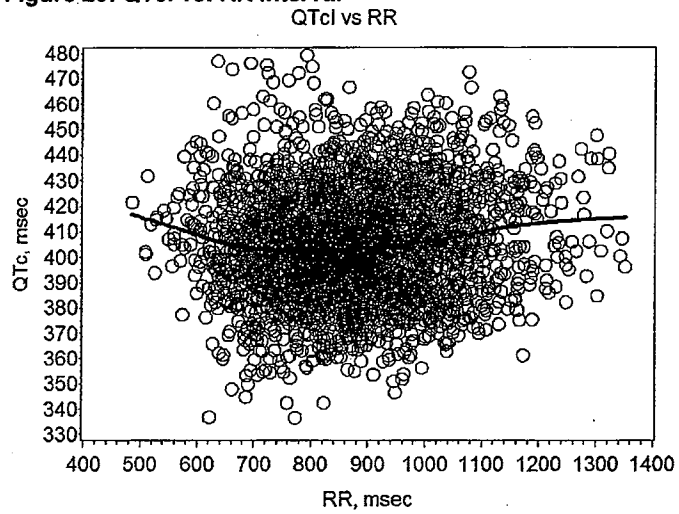


Table 57: QTcI-RR analysis results

Obs	Intercept	Effect	Estimate	StdErr	DF	tValue	Probt
1	387.55 ms	RR (ms)	0.01966	0.00180	260	10.95	<.0001

Figure 27: QTcF vs. RR interval

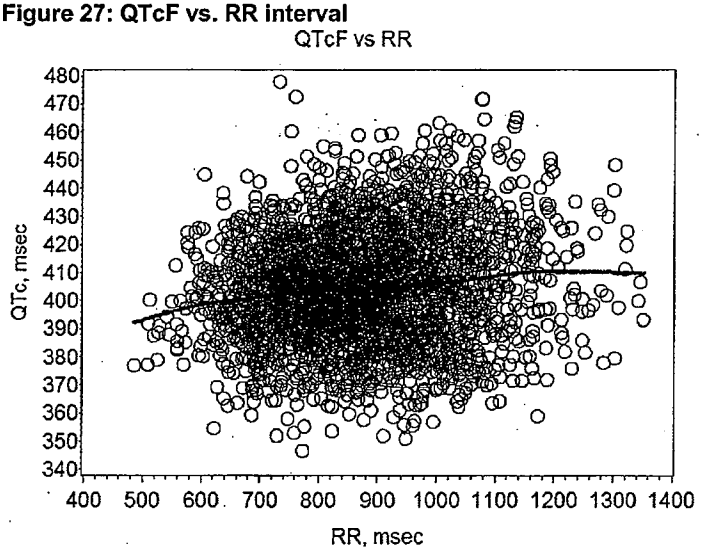


Table 58: QTcF-RR analysis results

Obs	Intercept	Effect	Estimate	StdErr	DF	tValue	Probt
1	387.82 ms	RR (ms)	0.01893	0.00215	260	8.81	<.0001

2. Pharmacokinetics:

SPM 7605 PK parameters were calculated for both Day 1 and Day 3. Cmax and AUC values were slightly higher in this study than in study SP 566 using the same doses and dosing schedule. The AUC and Cmax achieved following the supratherapeutic dose of 28 mg in this study are greater than or about equal to those observed in a likely worse case scenario of a CYP2D6 PM taking a strong CYP3A4 inhibitor and 8 mg fesoterodine ER. Therefore, the doses given and exposure achieved are appropriate to characterize the effect of the standard dose of 4 mg fesoterodine and a likely worse case situation.

Table 59: Summary of SPM 7605 PK parameters (SP 686)

		Feso 4mg/day		Feso 28mg/day	
		Day 1 N=64	Day 3 N=64	Day 1 N=67	Day 3 N=64
Parameter	Unit	Mean (CV)			
$AUC_{0-t,ss}$	ng/mL*h	24.4 (41.3)	28.6 (38.0)	212.4 (40.8)	242.5 (44.6)
$AUC_{0-t,ss,\ norm}$	ng/mL*h*kg	1661 (41.5)	1953 (39.1)	14747 (41.3)	16802 (44.8)
$C_{max,ss}$	ng/mL	2.38 (38.1)	2.66 (33.3)	18.1 (40.9)	20.7 (40.0)
$C_{max,ss,norm}$	ng/mL*kg	162.5 (38.3)	181.7 (33.4)	1259.5 (43.0)	1435.1 (40.1)
$t_{max,ss}$	h	3.4 (53.1)	3.4 (40.2)	4.1 (36.1)	4.1 (36.7)
CL/f	L/h	212.8 (74.7)	177.1 (84.1)	155.2 (44.4)	182.2 (202.6)

CV = coefficient of variation of mean; Feso = fesoterodine; PKS = pharmacokinetic set

Table 60 shows the PK parameters for the metabolites SPM 5509, 7789, and 7790. The observed AUC and C_{max} in this study for 28 mg dose surpass the highest mean exposure of each respective metabolite observed in phase 1 intrinsic and extrinsic effect studies using the proposed dose of 8 mg fesoterodine.

Table 60: summary of metabolite PK parameters (SP 686)

		Feso 4mg/day		Feso 28mg/day	
		Day 1 N=64	Day 3 N=64	Day 1 N=67	Day 3 N=64
Parameter	Unit	Mean (CV)			
SPM 5509					
$AUC_{0-t,ss}$	ng/mL*h	99.5 (41.5)	126.8 (33.3)	826.2 (32.6)	1033.4 (31.3)
$AUC_{0-t,ss,\ norm}$	ng/mL*h*kg	6798 (40.5)	8710 (34.9)	57144 (31.5)	71582 (30.5)
$C_{max,ss}$	ng/mL	7.73 (45.3)	9.19 (31.9)	56.82 (33.6)	71.93 (34.6)
$C_{max,ss,norm}$	ng/mL*kg	531.8 (45.7)	632.6 (33.8)	3923.8 (31.4)	4973.8 (32.9)
$t_{max,ss}$	h	5.1 (41.6)	4.9 (37.2)	6.2 (31.3)	5.6 (37.1)
CL/f	L/h	48.8 (50.2)	35.9 (41.5)	38.8 (52.2)	38.0 (186.9)
SPM 7789					
$AUC_{0-t,ss}$	ng/mL*h	0.6 (106.0)	0.8 (95.4)	8.7 (64.0)	11.2 (70.0)
$AUC_{0-t,ss,\ norm}$	ng/mL*h*kg	40 (100.3)	50 (89.6)	594 (62.9)	770 (71.1)
$C_{max,ss}$	ng/mL	0.16 (30.4)	0.17 (28.0)	0.82 (42.4)	1.00 (48.3)
$C_{max,ss,norm}$	ng/mL*kg	10.1 (34.3)	11.1 (29.9)	56.4 (39.9)	68.8 (48.4)
$t_{max,ss}$	h	3.6 (58.4)	3.3 (37.2)	4.2 (46.3)	4.4 (38.4)
CL/f	L/h	25078.3 (113.7)	12895.4 (135.6)	5353.9 (78.7)	4514.7 (87.5)
SPM 7790					
$AUC_{0-t,ss}$	ng/mL*h	41.9 (48.9)	52.5 (43.0)	387.5 (45.4)	499.5 (43.9)
$AUC_{0-t,ss,\ norm}$	ng/mL*h*kg	2811 (42.4)	3535 (38.3)	26499 (40.5)	34286 (39.5)
$C_{max,ss}$	ng/mL	3.08 (45.9)	3.71 (37.5)	25.27 (45.3)	33.27 (46.5)
$C_{max,ss,norm}$	ng/mL*kg	208.3 (41.2)	250.9 (33.2)	1724.8 (39.4)	2278.7 (41.4)
$t_{max,ss}$	h	5.2 (42.8)	4.9 (44.1)	7.0 (46.5)	5.6 (38.9)
CL/f	L/h	124.6 (73.2)	92.9 (48.9)	87.6 (53.6)	88.0 (212.3)

CV = coefficient of variation of mean; Feso = fesoterodine; PKS = pharmacokinetic set

3. Effect on QT (Review of Sponsor's analysis):

Only the primary analysis using QTcF will be discussed in details. Analysis of QTcI yielded similar negative results. Bazett's correction method was not considered reliable and not reviewed.

Time-average change in QTcF:

The 24-hour average QTcF change from baseline (table 61) was negative for both doses of fesoterodine and was also very similar to placebo, suggesting that fesoterodine did not have effect on prolonging the QT interval. This method of calculation tends to suppress the magnitude of change from baseline, but since the change was in the negative direction it is not a concern. The 24-hour average QTcF change from baseline for the positive control moxifloxacin was 4.9 (95% CI 3.4 – 6.3) msec on day 1 and 8.6 (95% CI 7.1-10.1) msec on day 3. These increases due to moxifloxacin is on the low end of moxifloxacin response but is likely due to taking the average over 24 hours and also since these were not placebo subtracted (due to a parallel study design).

Table 61: 24-hour time-averaged QTcF by day (SP686)

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)

CI = confidence interval of mean; Feso = fesoterodine; Min = minimum; Max = maximum; ms = millisecond; PDS = pharmacodynamic set; SD = standard deviation
Data source: Table 8.1.1

Time-matched mean change in QTcF:

Figure 28 shows the mean baseline QTcF and figures 29 & 30 show the time-matched baseline-subtracted QTcF on Day 1 and 3, respectively, for all 4 treatment groups. Moxifloxacin had the lowest baseline and fesoterodine 4mg had the highest baseline throughout the 24 hour period. This may confound the comparison of baseline corrected values from these groups if these baselines are biased. However, it is reassuring that the 28 mg fesoterodine group generally had baseline corrected QTcF that was less than or equal to the 4 mg fesoterodine group (figure 30) even though it had average baseline that was lower than the 4 mg fesoterodine group, suggesting a lack of effect of any difference in baseline and that there is a lack of apparent positive dose-response on QT interval at doses up to 28 mg/day.

The time-matched difference from baseline QTcF on Days 1 and 3 were similar among placebo, 4 mg fesoterodine, and 8 mg fesoterodine. The time matched differences from baseline were also generally resulted in a negative change from baseline. The maximum mean change occurred at 10 hour post dose with placebo having the largest increase on Day 1 and all 3 groups having similar peak on Day 3. furthermore the maximum mean changes for these 3 groups were all less than 5 msec. The positive control had maximum mean change from baseline greater than 10 msec on Day 1 and greater than 15 msec on Day 3, indicating the method is sensitive. The data from time-matched analysis of QTcF suggests that fesoterodine does not have an effect on QT interval at doses tested.

Figure 28: time-matched mean QTcF at Baseline (SP 686)

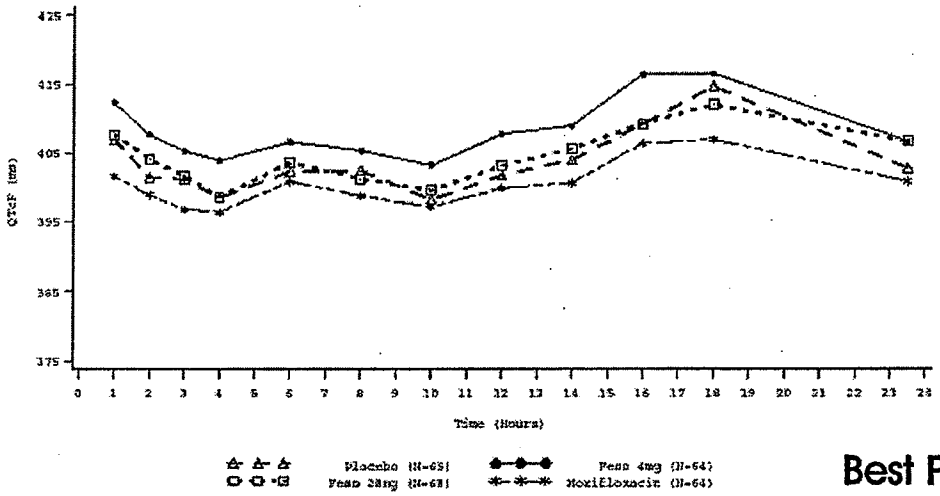


Figure 29: time-matched difference from Baseline in QTcF on Day 1 (SP 686)

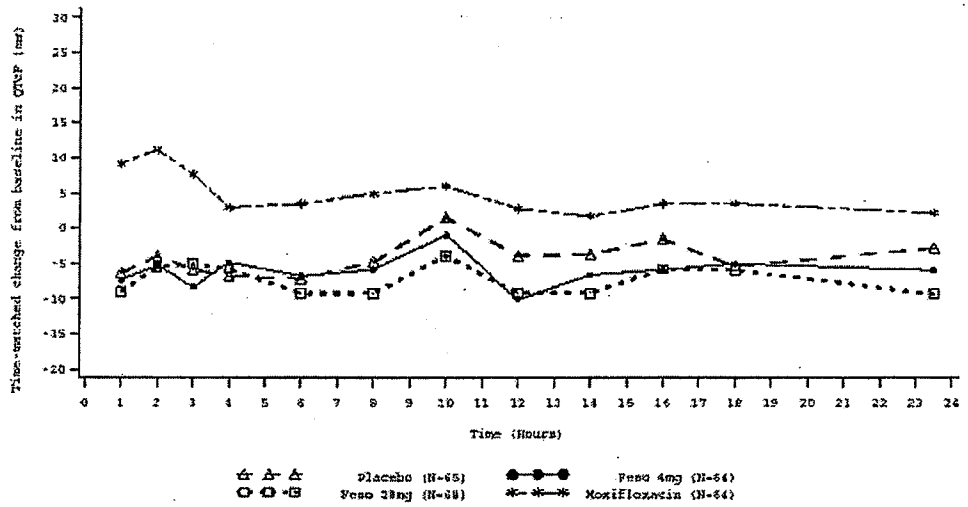
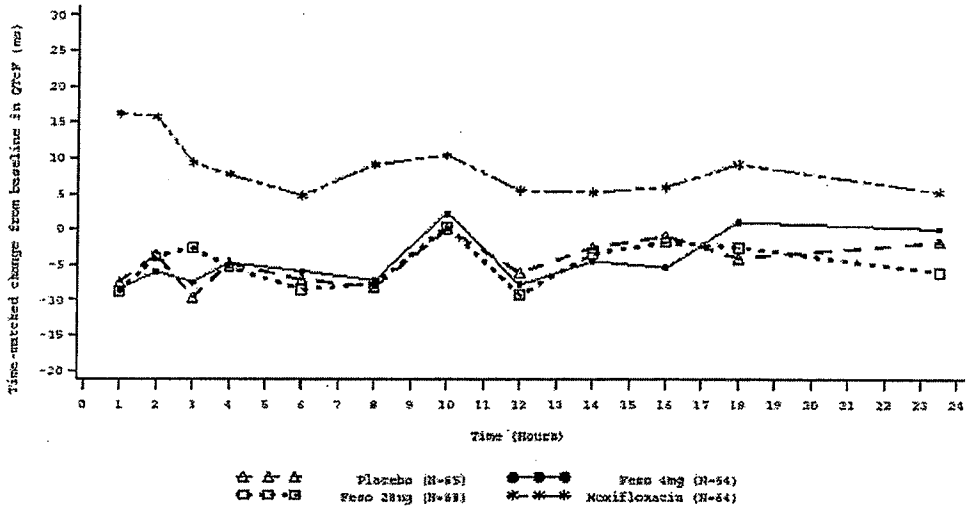


Figure 30: time-matched difference from Baseline in QTcF on Day 3 (SP 686)



Maximum change (mean max):

The maximum change in an ECG parameter is defined in the SAP as the maximum time matched change from Baseline observed for each subject across Days 1 and 3. This method is upwardly biased and is likely to produce a positive effect in all cases and thus is only being used to explore differences between groups and the actual magnitude of each group is not emphasized. Any significant change in the magnitude would be captured in the outlier analyses.

The mean maximum change from time-matched Baseline was similar among placebo and the 2 fesoterodine groups with placebo being highest at 21.4 msec. Moxifloxacin's effect was higher at 32.2 msec and was significantly higher than the other 3 groups. In conclusion, the analysis of maximum change confirmed assay sensitivity and suggest fesoterodine 4 and 28 mg did not have an effect on QT interval that differ from placebo.

Table 62: Summary of maximum change in QTcF (msec) (SP686)

Summary of maximum change in QTcF (ms) (PDS in SP686)

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)

CI = confidence interval of mean; Feso = fesoterodine; Min = minimum; Max = maximum; PDS = pharmacodynamic set; SD = standard deviation
Data source: Table 8.3.1

Outlier analysis:

Table 63 shows the QTcF outlier analysis for all treatment groups. For QTcF >450msec or >500 msec, the post-baseline values exclude all patients that were outlier at baseline.

No subject in any treatment group had QTcF > 500 msec. For QTcF > 450 msec, the proportion of subject that were outliers was similar among placebo and the 2 fesoterodine groups either

post-baseline or combined baseline and post-baseline. Moxifloxacin had a higher proportion at post-baseline that was >450 msec but still relatively small (11.1%).

In the placebo and fesoterodine groups, no subject had increase in QTcF > 60 msec and a similar proportion in each group had increase of >30 msec (15 – 19%). Moxifloxacin positive control showed 1 subject (1.6%) with QTcF increase > 60 msec and 32 (50%) with increase of 30 – 60 msec.

Table 63: QTcF outlier analysis

Finding Visit	Placebo N=65	Feso 4mg N=64	Feso 28mg N=68	Moxifloxacin N=64
QTcF > 450ms				
Baseline	3/65 (4.6)	7/64 (10.9)	4/68 (5.9)	1/64 (1.6)
Post-Baseline	3/62 (4.8)	2/57 (3.5)	0/64	7/63 (11.1)
QTcF > 500ms				
Baseline	0/65	0/64	0/68	0/64
Post-Baseline	0/65	0/64	0/68	0/64
Increase of QTcF 30-60ms	10/65 (15.4)	12/64 (18.8)	12/68 (17.6)	32/64 (50.0)
Increase of QTcF >60ms	0/65	0/64	0/68	1/64 (1.6)

Table 64 shows the post-baseline outlier analyses for all correction method. The QTcI method showed higher proportion of outlier at the > 450 msec and >480 msec cut-offs compared to QTcF. However, the same conclusion that fesoterodine is not different (worse) than placebo still hold true.

Table 64: summary of subjects with a new onset QT or QTc outlier value. Subjects that had outlier QT or QTc value at baseline were excluded. (SP 686)

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

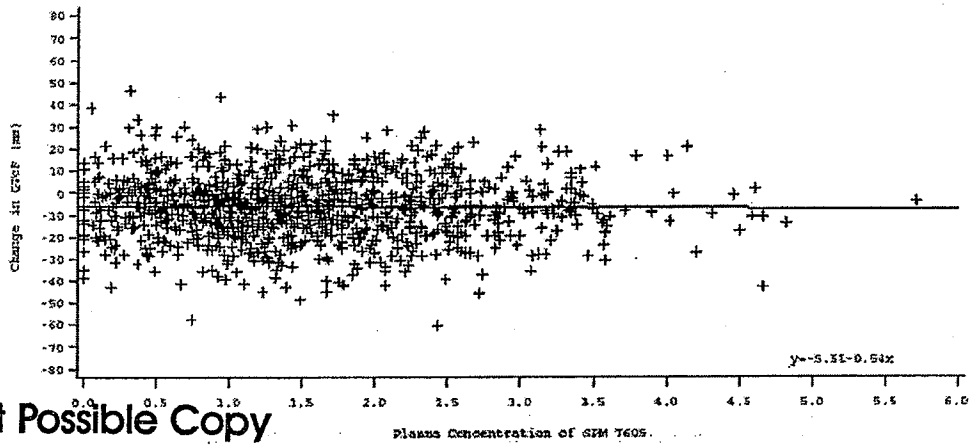
Feso = fesoterodine; Moxi = moxifloxacin; PDS = pharmacodynamic set

Correlation of SPM 7605 plasma concentration and change in QTcF:

Figure 31 and 32 show the correlation between SPM 7605 plasma concentration and Baseline subtracted QTcF value at time of PK measurement. The slope of the regression line is close to zero, indicating there is no correlation between SPM 7605 plasma concentration and change in QTcF.

Figure 31

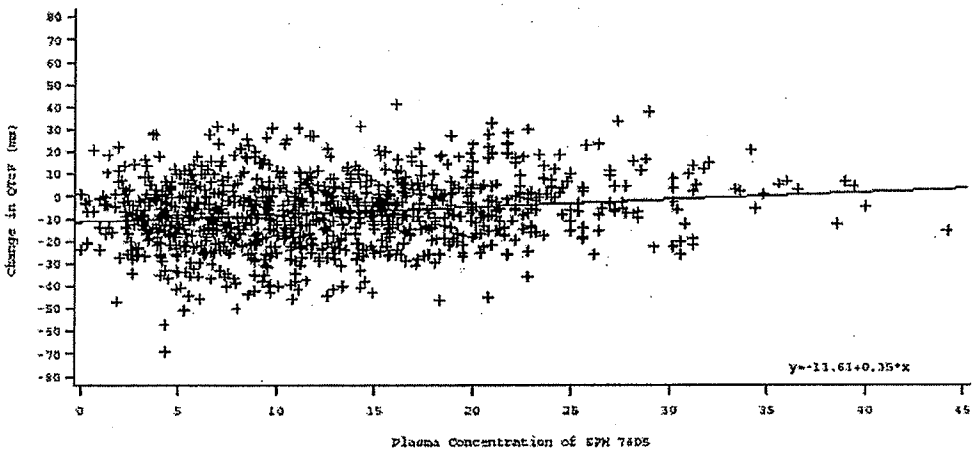
Correlation of change in QTcF and plasma concentration of SPM 7605 (ng/mL) – Fesoterodine 4mg/day (PKS in SP686)[a]



PDS = pharmacodynamic set; PKS = pharmacokinetic set
a Data are from the intersection of PDS and PKS, which in this trial is represented by the PKS

Figure 32

Correlation of change in QTcF and plasma concentration of SPM 7605 (ng/mL) – Fesoterodine 28mg/day (PKS in SP686)[a]



PDS = pharmacodynamic set; PKS = pharmacokinetic set
a Data are from the intersection of PDS and PKS, which in this trial is represented by the PKS

Figures 33 and 34 show the mean change in QTcF and mean plasma concentration of SPM 7605 over time on Day 3. They shows that SPM 7605 profiles were as expected with an increase to reach Cmax and followed by a decline in concentration. At the same time, changes in QTcF appear quite stable.

Figure 33: Mean change in QTcF and mean plasma concentration of SPM 7605 over time following 4 mg fesoterodine on Day 3.

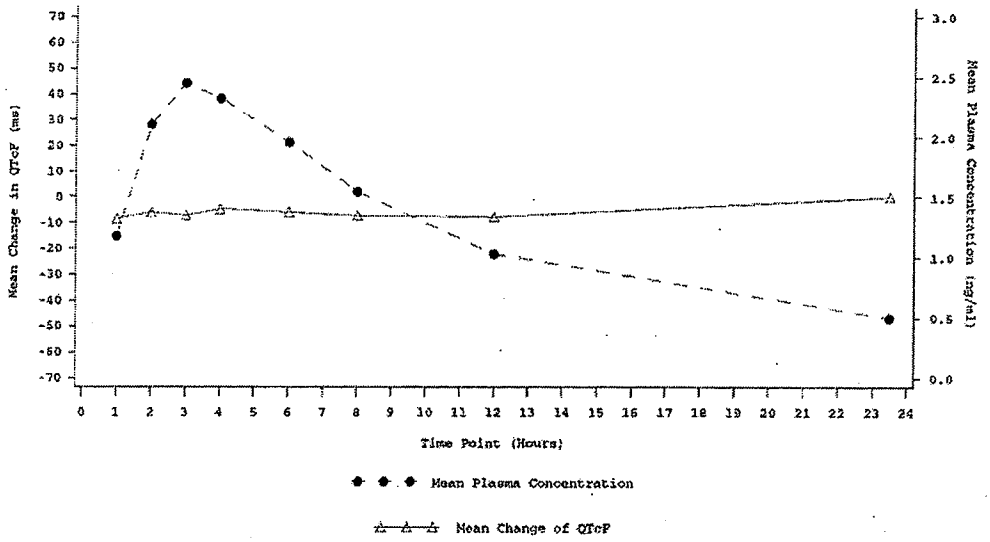
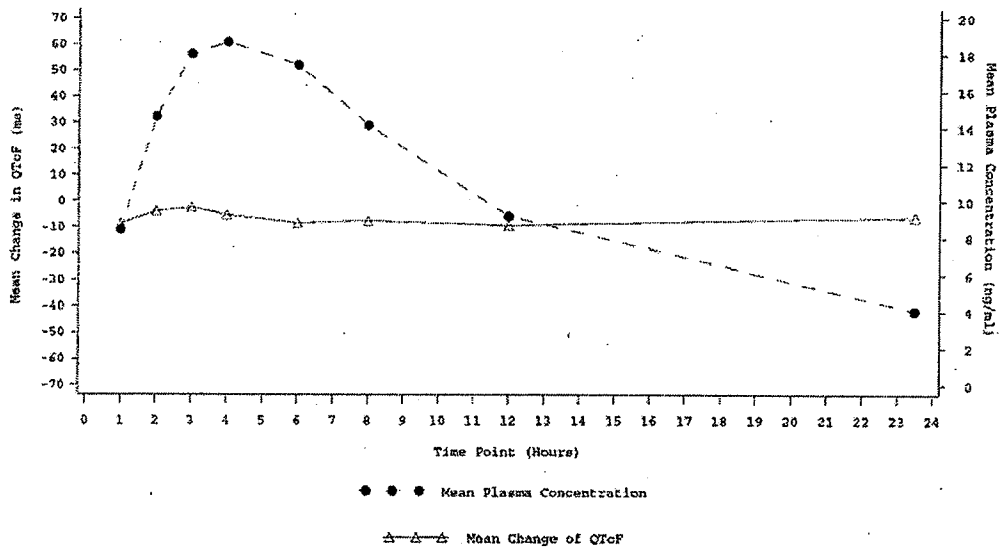


Figure 34: Mean change in QTcF and mean plasma concentration of SPM 7605 over time following 28 mg fesoterodine on Day 3.



4. Effect on QT – Additional analysis by FDA

We calculated the difference and 90% CI between the least square means of baseline-corrected time-matched QTc for placebo and each fesoterodine treatment groups and positive control moxifloxacin.

Maximum mean effect of moxifloxacin on Day 1 on QTcF was 15.5 msec (upper 95% CI 19.6) occurring at 1 hour and the effect on QTcI was 15.6 msec (upper 95% CI 20.0) occurring at 2 hour. Moxifloxacin effects were also positive for all time points up to 8 hour using either correction methods.

The two tables below show the placebo and baseline corrected effect (ddQTc) of fesoterodine on QTcF and QTcI, respectively. The data shows that 4 mg fesoterodine did not have the upper 95% CI of QTc exceeding 10 ms. The maximum QTc effect was observed at the 18 hour time point, when concentration of fesoterodine is expected to be very low. For fesoterodine 28 mg dose, the 10 msec was exceeded at only one time point and only with QTcF, i.e., at 3 hours in the QTcF analysis. It is not clear if this is a true positive effect since the 2 hour and 4 hour time points (i.e., immediately before and after) both have negative mean QTc effect with upper 95% CI <4 msec. Additionally, the mean T_{max} observed in this study on was 4.1 hour for the 28 mg dose.

Table 65: ddQTcF by time and group on Day 3 (group 1=4 mg fesoterodine, 2=28 mg fesoterodine)

Obs	HOUR	group	Estimate	Upper
1	1	1	-1.0915	3.0057
2	2	1	-2.4382	1.6757
3	3	1	2.1448	6.2420
4	4	1	0.04233	4.1556
5	6	1	1.1926	5.3235
6	8	1	1.0106	5.1239
7	10	1	2.1746	6.2879
8	12	1	-1.6929	2.4370
9	14	1	-1.8836	2.2297
10	16	1	-4.4561	-0.3092
11	18	1	5.0660	9.1632
12	23.5	1	1.8667	6.0300
13	1	2	-1.3906	2.6904
14	2	2	-0.2258	3.8880
15	3	2	6.9937	11.0909
16	4	2	-0.5614	3.5685
17	6	2	-1.3616	2.7853
18	8	2	0.5025	4.5997
19	10	2	0.2967	4.4266
20	12	2	-3.1309	0.9663
21	14	2	-0.8201	3.2932
22	16	2	-0.8607	3.3026
23	18	2	1.5035	5.6007
24	23.5	2	-4.2438	-0.04513

Table 66: ddQTcI by time and group on Day 3 (group 1=4 mg fesoterodine, 2=28 mg fesoterodine)

Obs	HOUR	group	Estimate	Upper
1	1	1	-0.3941	4.0871
2	2	1	-2.1744	2.3250
3	3	1	0.9735	5.4547
4	4	1	-0.6530	3.8458
5	6	1	1.6782	6.1962
6	8	1	0.1541	4.6529
7	10	1	0.5848	5.0836
8	12	1	-1.6977	2.8192
9	14	1	-2.4121	2.0868
10	16	1	-4.5691	-0.03356
11	18	1	4.1961	8.6773
12	23.5	1	2.0443	6.5978
13	1	2	-2.4738	1.9897
14	2	2	-1.4530	3.0464
15	3	2	4.6114	9.0926
16	4	2	-4.3132	0.2037
17	6	2	-1.8186	2.7170
18	8	2	-1.9529	2.5283
19	10	2	-1.7399	2.7770
20	12	2	-4.5208	-0.03963
21	14	2	-2.1597	2.3391
22	16	2	-1.6029	2.9506
23	18	2	-0.1277	4.3535
24	23.5	2	-5.6665	-1.0743

We also conducted concentration-ddQTc analysis to estimate the QTc effect. Our analysis assumes that there is a direct effect of fesoterodine concentration on QTc interval. The results are shown in the plots below.

Figure 35: SPM 7605 concentration-ddQTcF analysis

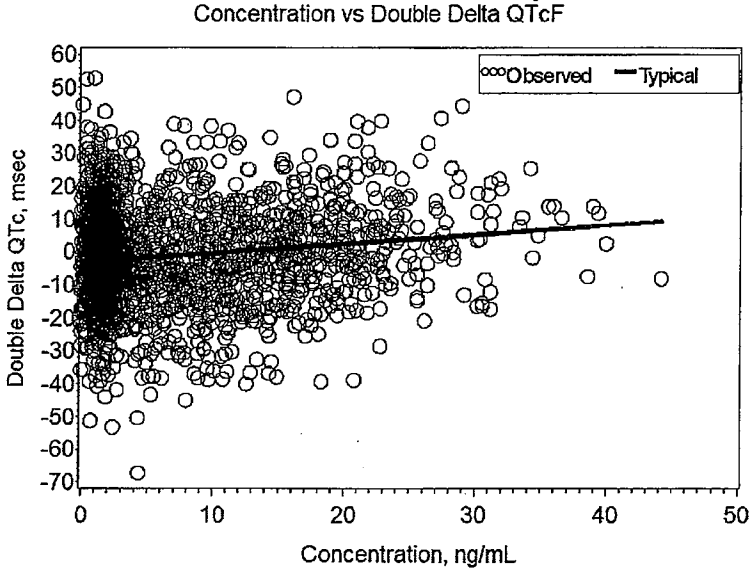


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Table 67: Concentration-QTcF analysis results

Obs	Effect	Estimate	StdErr	DF	tValue	Probt	Upper 95% CI for slope	Upper 95% CI QT effect of 4 mg	Upper 95% CI QT effect of 28mg
1	SPM 7605 concentration	0.2768	0.06471	131	4.28	<.0001	0.38325	1.01945	7.93334

Concentration-ddQTcF analysis shows a small positive response due to fesoterodine concentration. However, the upper 95% CI effect, based on observed mean C_{max}, was 1.0 and 7.9 msec for 4 mg and 28 mg fesoterodine, respectively. This indicates no significant effect on QTcF at doses up to 28 mg/day.

Figure 36: SPM 7605 concentration-ddQTcI analysis

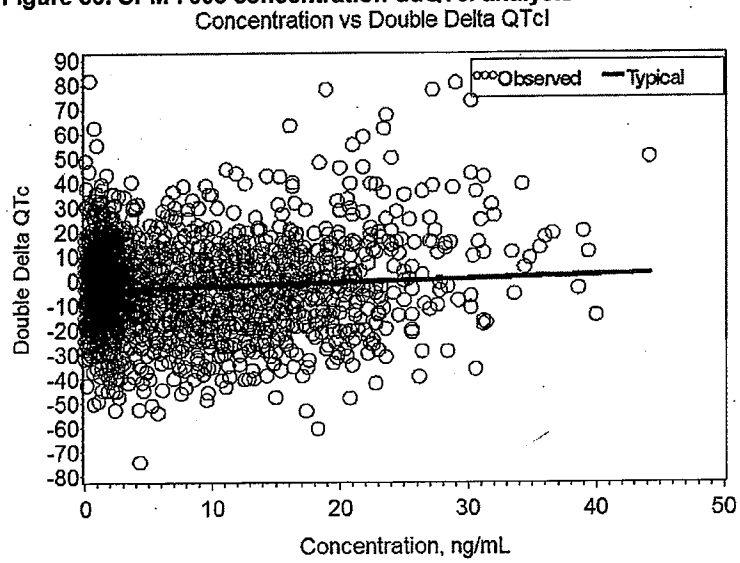

Table 68: Concentration-QTcI analysis results

Obs	Effect	Estimate	StdErr	DF	tValue	Probt	Upper 95% CI for slope	Upper 95% CI QT effect of 4 mg	Upper 95% CI QT effect of 28 mg
1	SPM 7605 concentration	0.1545	0.1131	131	1.37	0.1742	0.34054	0.90584	7.04918

Concentration-ddQTcI analysis also shows a small positive response due to fesoterodine concentration. However, the upper 95% CI effect, based on observed mean C_{max}, was 0.9 and 7.0 msec for 4 mg and 28 mg fesoterodine, respectively. This indicates no significant effect on QTcI at doses up to 28 mg/day.

5. Effect on heart rate:

As expected due to its antimuscarinic properties fesoterodine caused a dose dependent increase in heart rate. The proportion of subjects that had heart rate increase of >25% and the increase resulted in HR >100bpm were 16.9%, 39.1%, 76.5%, and 23.4% for placebo, 4 mg fesoterodine, 28 mg fesoterodine, and moxifloxacin, respectively.

Figures 35 and 36 show the heart rate change from time-matched Baseline on Day 1 and 3. The 28 mg fesoterodine dose caused a mean increase in heart rate of about 25 bpm from 2 – 8 hour post dose on Day 1 and about 22 bpm above Baseline on Day 3.

Figure 37: Change from Baseline in heart rate on Day 1

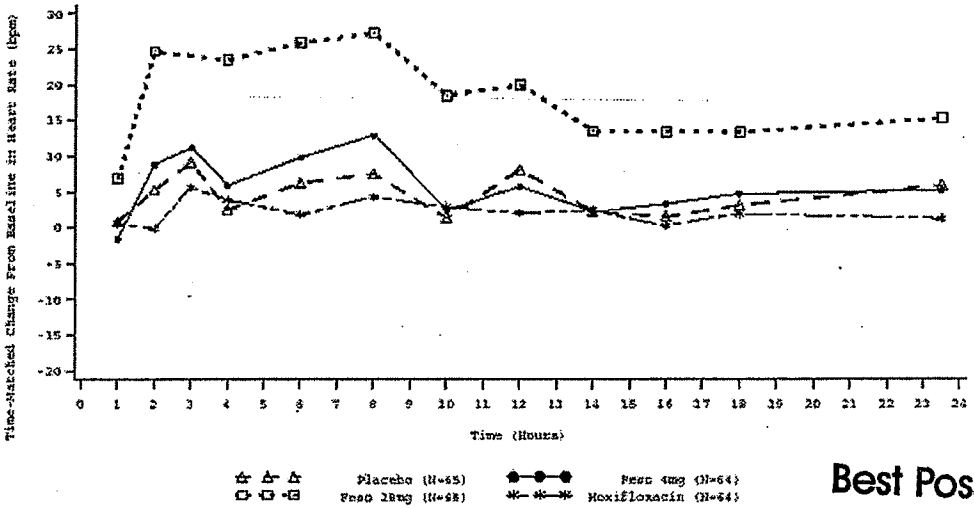

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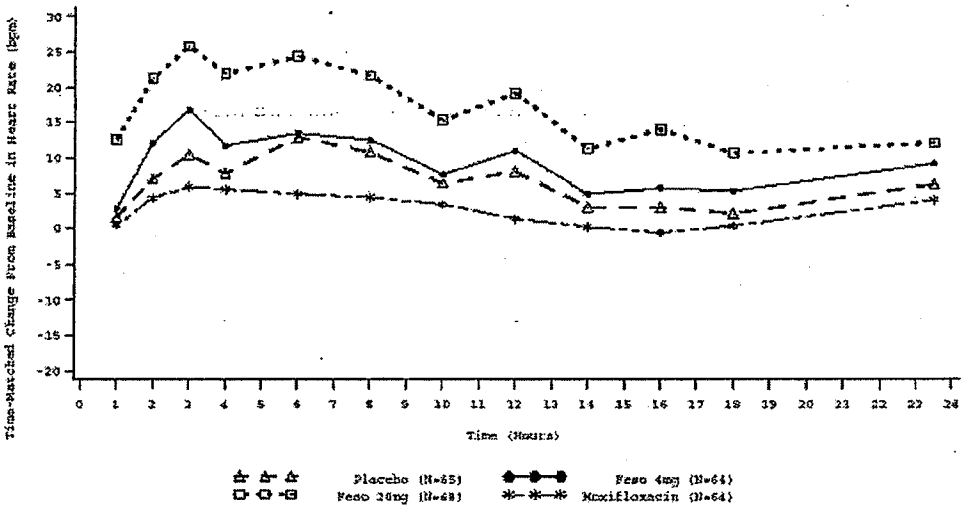
Figure 38: Change from Baseline in heart rate on Day 3



In conclusion, fesoterodine 4 and 28 mg/day for 3 days did not appear to have a significant effect on QTc interval. Time matched ddQTcF analysis showed 28 mg significantly increased QTcF at 3 hour. However, this was likely due the sharp decrease observed in the placebo group because no positive effect was observed at any other time points including the one immediately before and after 3 hour and T_{max}. Futhermore, concentration-QTc analysis indicated that 28 mg fesoterodine should not significantly affect QTc interval. Fesoterodine did have a dose dependent effect on increasing heart rate with the 28 mg dose causing a sustained increase in heart rate of ≥ 23 bpm.

Of note to the safety of fesoterodine, the 28 mg dose was previously determined in SP 566 to be the maximum tolerated dose due to urinary retention. In this study, one subject in the 28 mg group also needed catherterization to relieve urinary retention.

Appendix 4.2.2:

This section list the parameter estimates for the final population PK model in each of the 3 pop PK studies. All models used one compartment, first order absorption, and first order elimination. Volume of distribution was normalized to population mean body weight.

SP 582:

No covariate was supported by data from SP 582. The covariates tested were age, gender, body weight, body height, creatinine clearance, and BMI (body mass index).

Table 69: Population PK parameter estimates of the final model in from SP 582

Parameter	Final estimate	SE of Final Estimate	Rel. SE of Final Estimate (%)
V/f (L x 10^3)	1.280	0.299	23.4
k_e (h^{-1})	0.0622	0.0110	17.7
k_a (h^{-1})	0.498	0.312	62.7

Parameter	ETA / IIV %	SE of ETA	Rel. SE of ETA (%)
V/f	0.0266 /16.3	0.0320	120.3
k_e	0.194 / 44	0.0456	23.5
k_a	0.658 / 81.1	0.876	133.1

SIGMA/EPS	Res. Error (%)	SE of EPS	Rel. SE of EPS (%)
0.281	53	0.039	13.9

SE=Standard error, ETA/IIV=Interindividual variability, SIGMA/EPS=Residual random error

SP 668:

The best fit was obtained with exponential inclusion of inter-individual variability on ka, ke and V/f. The inclusion of a lag-time (=time until measurable concentrations in central compartment) did significantly improve the fit. Thus, the minimum of objective function is provided with exponential inclusion of inter-individual variability on ka, ke and V/f, inclusion of a lag-time and an exponential residual error model. This is the base model.

Most covariates were ruled out by graphical evaluation. A few promising candidates were tested by modeling. The only covariate found to be statistically significant was CYP2D6 PM on V/f. However, this only reduced the inter-individual variability slightly from 44% to 41%. The sponsor attributed this to the low number of PM subjects (8 of 111) in this study. The model still contains a high residual error of 46% indicating a large portion of the variability cannot be explained. The following potential covariates were considered: age, gender, race, sex, body weight, body height, BMI, CYP2D6 PM or EM status, creatinine, creatinine clearance, glumerular filtration rate, total bilirubin, GGT (gamma glutamyl transferase), GOT (glutamic-oxaloacetic transaminase), GPT (glutamic-pyruvic transaminase), and ALP (alkaline phosphatase).

Table 70: Population PK parameter estimates of the final model in SP 668

Final population parameter estimates

Parameter	Status of CYP 2D6	Final estimate	Rel. SE of final estimate [%]
V/f [L]	Extensive	1640	8.8
V/f [L]	Poor	1219	8.8
k_e [h^{-1}]	---	0.0694	8.4
k_a [h^{-1}]	---	1.56	20

Parameter	Inter-individual variability [%]	Rel. SE of IIV [%]
V/f	40.9	38.8
k_e	26.6	46.5
k_a	85.7	44.9

SIGMA/EPS	Residual error [%]	Rel. SE of residual error [%]
0.211	45.9	41.9

SE=Standard error, SIGMA/EPS=Residual random error, IIV=Inter-individual variability

SP 584:

The final equations to approximate the PK parameters CL/f, V/f and ka for each individual within the study population are:

TVCL = 0.00305 -0.0273*poor + 0.154*(HT/165.5) -0.000360*ALP -0.000825*GGT

TVV = 1.43 * WT/80.95+ 0.751*TB

TVKA = THETA(3)

Most of the CL/f (with the dimension 10^3 L/h) of the study population (TVCL) is described by the ratio HT/165.5 and the factor 0.154. Most of V/f (with the dimension 10^3 L) is described by the body weight normalization of factor 1.43. ka is described by the population parameter TVKA with no covariate.

The following potential covariates were considered: age, gender, body weight, body height, CYP2D6 PM or EM status, creatinine clearance, total bilirubin (TB), GGT (gamma glutamyl transferase), AST (aspartate amino transferase), and ALP (alkaline phosphatase).

Table 71: Population PK parameter estimates of the final model in SP 584

Parameter	Final Estimate	SE of Final Estimate	Rel. SE of Final Estimate [%]
CL/f [1000*L/h]	0.00305	0.102	33400
V/f [1000*L]	1.43	0.235	16.4
k_a [h^{-1}]	0.658	0.362	55.0
CYP2D6 genotype on CL/f	-0.0273	0.00126	46.2
HT on CL/f	0.154	0.0983	63.8
ALP on CL/f	-0.000360	0.000103	28.6
GGT on CL/f	-0.000825	0.000196	23.8
Total bilirubin on V/f	0.752	0.446	59.3
Parameter	ETA (IIV) / IIV [%]	SE of ETA	Rel. SE of ETA [%]
CL/f [L/h]	0.227/47.6	0.0603	26.6
V/f [L]	0.026/16.1	0.145	558
k_a [h^{-1}]	1.33/115	0.683	51.4
SIGMA/EPS	Res. Error [%]	SE of EPS	Rel. SE of EPS [%]
0.0569 0.291	0.239 53.9	0.107 0.0525	188 18.0

SE=Standard error, ETA/IIV=Inter-individual variability, SIGMA/EPS=Residual error

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