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Thorough QT study of the effect of fesoterodine on cardiac repolarization

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Key words
OAB – fesoterodine – cardiovascular safety – antimuscarinic

Abstract. Objective: Fesoterodine 4 mg and 8 mg once daily are indicated for the treatment of overactive bladder. A thorough QT study was conducted to investigate the effects of fesoterodine on cardiac repolarization. Materials and methods: In this parallel-group study, subjects were randomly assigned to receive double-blind fesoterodine 4 mg, fesoterodine 28 mg, or placebo or open-label moxifloxacin 400 mg (positive control) for 3 days. Electrocardiograms (ECGs) were obtained on Days –1 (baseline), 1, and 3. The primary analysis was the time-averaged changes from baseline for Fridericia's-corrected QT interval (QTcF) on Day 3. Results: Among 261 subjects randomized to fesoterodine 4 mg (n = 64), fesoterodine 28 mg (n = 68), placebo (n = 65), or moxifloxacin 400 mg (n = 64), 256 completed the trial. The least squares mean changes in QTcF from baseline were 21.1, 20.5, 18.5, and 31.3 ms (maximum), and –5.1, –4.2, –5.2, and 7.6 ms (time-averaged at Day 3) for placebo, fesoterodine 4 mg, fesoterodine 28 mg, and moxifloxacin, respectively. The lower limit of the 95% confidence interval exceeded 5 ms for moxifloxacin. Conclusions: The results indicate that fesoterodine is not associated with QTc prolongation or other ECG abnormalities at either therapeutic or supratherapeutic doses.

Introduction

Fesoterodine is a new antimuscarinic agent that has demonstrated safety and efficacy for the treatment of overactive bladder (OAB) [2, 10]. Fesoterodine is not detectable in plasma following oral administration; it is rapidly and extensively converted by nonspecific esterases to the active metabolite 5-hydroxymethyl tolterodine (5-HMT) (Figure 1), which is also the active metabolite of tolterodine [15]. The mean plasma half-life of 5-HMT is approximately 8 hours after administration of fesoterodine 4 mg and 9 hours after administration of fesoterodine 8 or 12 mg in a fasted state; these values are similar in extensive metabolizers and poor metabolizers [8, 14].

Thorough QT studies have become part of the drug development process, as a standard regulatory requirement for assessing the effect of a drug on cardiac repolarization and determining its proarrhythmic potential [3]. The QT interval prolongation (the time for electrophysiologic depolarization and repolarization of ventricles) may be a characteristic of torsade de pointes, which has been documented to occur beyond threshold limits of > 500 ms corrected QT interval (QTc) and > 60 ms QTc prolongation and, as such, is a risk factor for ventricular arrhythmia and sudden death [11]. Cardiac safety concerns due to drug-related QT interval prolongation have been the reason some drugs have been withdrawn from the pharmaceutical market [11]. For example, the antimuscarinic agent terodiline (1991) [4, 7, 13] and the antihistamine terfenadine (1998) [5] were removed from the market by the United States Food and Drug Administration because of associated electrocardiographic (ECG) effects, including drug-induced proarrhythmia.

No clinically relevant effects on the QTc interval have been previously reported in Phase I, II, and III clinical trials of fesoterodine in healthy volunteers or subjects with OAB [2, 12]. Similarly, no clinically relevant cardiac effects were observed at single doses of 4 mg, 8 mg, and 12 mg in a pharmacokinetic study in healthy volunteers that demonstrated a 2-fold increase in exposure to 5-HMT in poor metabolizers compared with extensive metabolizers [8]. Because these Phase I studies of fesoterodine were not specifically designed to determine the effect of fesoterodine on cardiac electrophysiology and QT interval, this thorough QT study was

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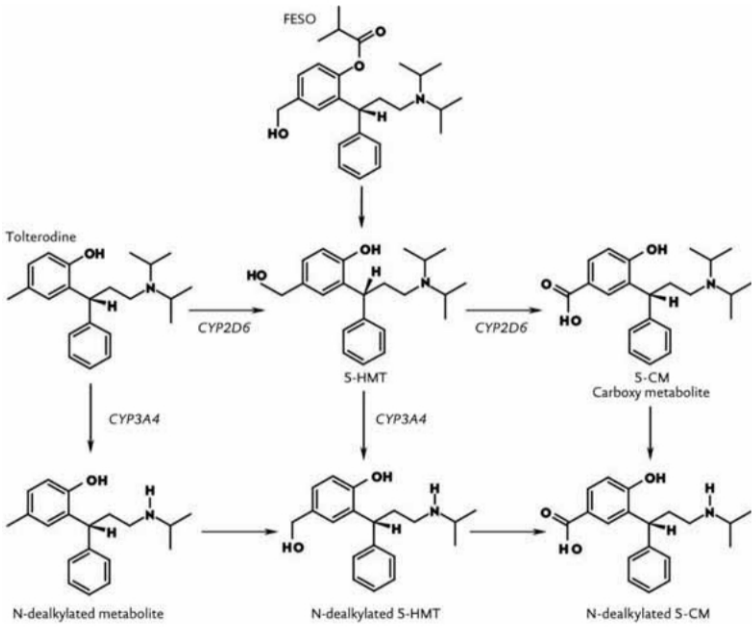

Figure 1. Fesoterodine (FESO) metabolic pathway. CYP = cytochrome P450; 5-HMT = 5-hydroxymethyl tolterodine.

conducted to investigate the effects of fesoterodine on cardiac repolarization.

The study was conducted in accordance with the International Conference on Harmonization (ICH)-E14 guidelines [3] for the evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. The guidelines dictate that a negative thorough QT study should demonstrate that the mean threshold for QT/QTc prolongation remains less than 5 ms and that the upper bound of the 95% 1-sided confidence interval for the largest time-matched mean effect on QT should exclude 10 ms. This placebo-controlled study was conducted at steady state after administration of a therapeutic (4 mg/day) or supratherapeutic (28 mg/day) dosage of fesoterodine for 3 days in healthy cytochrome P450 (CYP) 2D6 extensive metabolizers and included moxifloxacin 400 mg as a positive control. The 28-mg/day dosage was selected because it was previously defined as the maximum tolerated dose of fesoterodine. Furthermore, plasma exposures after a 28-mg/day dosage of fesoterodine are appropriate to cover a "worst case scenario" of exposure in a CYP2D6 poor metabolizer receiving fesoterodine 8 mg/day plus a potent CYP3A4 inhibitor, based on the results of a previously conducted drug interaction study in healthy volunteers [9].

Because the terminal half-life of 5-HMT after oral administration is approximately 8 – 9 hours [9], administering fesoterodine once daily for 3 days is appropriate for evaluating the QTc effects of fesoterodine at steady state. Although both crossover and parallel-group study designs are suitable for thorough QT evaluations, we chose a parallel-group design for this 4-treatment study to minimize the anticipated subject drop-out rate and to allow rapid completion of the trial [3]. Overall, the duration of dosing and the dosage of fesoterodine were suitable to allow characterization of QTc effects at 5-HMT concentrations expected in the possible clinical situation of a CYP2D6 poor metabolizer receiving the highest therapeutic dose of fesoterodine along with a potent CYP3A4 inhibitor.

Methods

Study design

This was a single-site, randomized, placebo- and positive-controlled, parallel-design trial with multiple oral dose administration of double-blind fesoterodine or placebo or open-label moxifloxacin. The treatment phase began 3 – 28 days after the eligibility assessment and consisted of 3 days of treatment as follows:

- 1 fesoterodine 4-mg sustained release (SR) tablet + 6 placebo tablets matching fesoterodine
- 7 fesoterodine 4-mg SR tablets
- 7 placebo tablets matching fesoterodine
- 1 moxifloxacin 400-mg tablet

Moxifloxacin is often used in thorough QT studies as a positive control because of its well-defined QT/QTc effect (5 – 14 ms) [11] and, as such, provides context for the sensitivity of the study to detect small QTc changes of around 5 ms [3].

Subjects

The trial protocol, amendments, and subject informed consent were reviewed by the appropriate Institutional Review Board (Independent Investigational Review Board Inc.). Informed consent was obtained from each subject and documented according to

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the current version of the applicable regulatory and ICH Good Clinical Practice requirements. The study was conducted under in-house conditions at SFBC International, a clinical research organization in Miami, FL, USA.

Key inclusion criteria were healthy subjects aged 45 – 65 years with a body mass index between 19 and 32 kg/m^2 (inclusive). Eligible subjects also had no clinically relevant abnormal findings on the physical examination, ECG, blood pressure, pulse rate, medical history, or clinical laboratory results at the eligibility assessment visit and were characterized as extensive metabolizers for CYP2D6. Key exclusion criteria were medical history of any serious disease of the internal organs or of the central nervous system; a history or presence of urinary retention, obstructive disturbance of bladder emptying, micturition disturbance, nocturia, or pollakiuria, for example, prostatic hyperplasia, or urethral stricture; a history of ischemic heart disease or a positive diagnostic cardiac stress test within 12 weeks before the start of the trial; a supine pulse rate of < 50 bpm or > 100 bpm, supine systolic blood pressure of < 100 mmHg or > 160 mmHg, or a supine diastolic blood pressure of > 95 mmHg; and any clinically relevant changes in ECG, such as second- or third-degree AV block, or prolongation of the QRS interval to > 110 ms, the PR interval to > 240 ms, or QTc (Bazett's correction, machine read) to > 480 ms.

ECG assessments

Electrocardiograms were obtained digitally using a Mortara Instrument H-12 ECG continuous recorder. The ECGs were stored on a flashcard approximately every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed. Electrocardiographic interval and morphology changes were based on change from baseline, where baseline was the mean of the 36 recordings obtained on Day –1. Triplicate 12-lead ECGs (within 1 minute) were obtained and averaged for each of the following time points: at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours postdose on Days 1 and 3 and at matching time points for baseline on Day –1, resulting in a total of 108 ECGs per subject. For practical purposes, it was necessary to have the last ECG collected at 23.5 rather than 24 hours postdose.

QTc interval analysis of ECGs

Centrally read ECG data were used to determine: (1) central tendency of QTc changes using maximum, time-averaged, and time-matched changes from baseline; and (2) outlier analyses. In addition, correlations of Frideri-ca's-corrected (QTcF), Bazett's-corrected QT interval (QTcB), and individually determined QT correction (QTcI) values with 5-HMT plasma concentrations were assessed.

The primary correction formula was QTcF, the length of the QT interval corrected for heart rate by Fridericia's formula: $QTcF = QT/(RR)^{1/3}$. Additional correction formulas that were included but considered secondary were QTcB and QTcI. The additional corrected QT interval QTcB is defined as the length of the QT interval corrected for heart rate by Bazett's formula: $QTcB = QT/(RR)^{1/2}$. The corrected QT interval (QTcI) was determined for each subject by iterating the QT-RR relationship using the 36 baseline ECGs (Day –1) to find an estimate for the exponent such that the slope of this relationship was closest to 0 or other appropriate method. The QTcI is the individually determined QT correction, and the goal was to find β such that QTcI is a constant, where $QTcI = QT/(RR)^{\beta}$. This implies $\log(QTcI) = \log(QT) - \beta \times \log(RR)$. Because log(QTcI) is a constant, this equation can be rewritten as $\log(QT) = \alpha + \beta \times \log(RR)$. Therefore, the exponent estimate can be obtained by numerical iteration such that slope for QT-RR relationship is closest to 0 or using regression analysis on log-transformed data based on the least squares (LS) approach.

Pharmacokinetic assessments

Venous blood samples were drawn from all subjects at the following time points on Days 1 and 3: predose (Day 1) and 1, 2, 3, 4, 6, 8, 12, and 23.5 hours postdose. Plasma was separated from the blood samples collected after fesoterodine treatments and stored frozen until the samples were sent to the bioanalytical unit of Schwarz BioSciences, Monheim, Germany. Plasma samples were

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assayed for 5-HMT using a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 0.04 ng/ml.

The pharmacokinetic variables assessed were area under the plasma concentration versus time curve from 0 to the last measured concentration greater than the lower limit of quantification during a dose interval at steady-state conditions (AUC_{0-t}); maximum drug concentration in plasma during a dose interval at steady state (C_{max}); time of observed C_{max} (t_{max}); and apparent total body clearance of drug.

Safety

Safety was monitored by assessing adverse events, vital signs, ECG recordings, and laboratory tests.

Statistical methods

Analyses were conducted in the pharmacodynamics population set, which included all randomized subjects who received at least one dose of trial medication and had a sufficient number of ECG assessments to calculate reliable estimates for the pharmacodynamic parameters.

For analyses of central tendency of QTcF changes (the primary variable), three methods were explored: maximum, time-averaged, and time-matched QTcF changes from baseline. The primary method was a time-averaged analysis on Day 3. The secondary methods were placebo-subtracted maximum and time-matched changes from baseline for QTcF on Day 3. For time-averaged analyses, the baseline corresponded to the mean of the 36 recordings obtained on Day –1, and for time-matched analyses the baseline corresponded to the mean of the three recordings obtained at the same time point on Day –1.

In the time-averaged analysis, all values within each sampling day were averaged to obtain a single value. This analysis averaged over any possible circadian rhythms. The mean time-averaged value was summarized by day and treatment group with descriptive statistics. For Days 1 and 3, change from baseline was summarized in a similar manner. For each treatment group, a 2-sided 95% confidence interval for the change from time-averaged baseline value on Days 1 and 3 was presented.

The second method for analysis was a time-matched analysis for which the mean value at each sampling time point (mean of three ECGs at that time point; there were 12 time points per day) was summarized by time point for baseline, Day 1, and Day 3 by treatment group with descriptive statistics. For Days 1 and 3, the time-matched change from baseline values was summarized by treatment group with descriptive statistics. In the time-matched change from baseline, each post-baseline value was compared with the corresponding value at baseline for that specific time point during the day.

The final method involved examining the maximum change from baseline. The maximum change from baseline was defined as the maximum time-matched change from baseline observed for each subject across Days 1 and 3. The maximum change from baseline in QTcF was summarized by treatment group with descriptive statistics. A 2-sided 95% confidence interval for maximum change from baseline was presented for each treatment group.

Time-averaged change from baseline and maximum change from baseline were analyzed in analysis of covariance (ANCOVA) models with gender and treatment group as factors, and the corresponding mean baseline value of ECG as a covariate. These analyses were exploratory, and each pair wise comparison of factor levels was performed at the 5% level of significance without multiplicity adjustment. 95% confidence intervals were derived for all pair wise mean differences between treatments (i.e., comparing each active treatment vs. placebo, the two fesoterodine dose groups vs. moxifloxacin, and the higher dose vs. lower dose for fesoterodine) using the LS means and corresponding residual error from the ANCOVA model. 90% confidence intervals (equivalent to 95% 1-sided confidence intervals) were also presented for the pair wise differences between treatments.

For the outlier analysis, the number and percentage of subjects who had an absolute QTcF of < 450, 450 to < 480, 480 to < 500, and ≥ 500 ms and the number and percentage of subjects who had an increase from baseline QTcF of < 30, 30 to < 60, and ≥ 60 ms were summarized by day, time point, and treatment

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group. This analysis was repeated by gender. The proportion of subjects meeting outlier criteria for each treatment group was computed using the longest of the triplicate ECG intervals at a given time point after treatment, compared with baseline values.

Although QTcF was the primary correction method for this trial, all analyses of QTcF were repeated for the secondary variables (QTcI, QTcB, uncorrected QT, heart rate, PR interval, QRS interval). All p values associated with QTcI are considered exploratory.

Because the ICH-E14 guidelines state that QTcB overcorrects at elevated heart rates and undercorrects at heart rates below 60 bpm, it is not an ideal correction for assessing the effects of fesoterodine on cardiac repolarization. Therefore, because Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates, only QTcF and QTcI results are presented.

Descriptive statistics were conducted for secondary safety endpoints, including adverse events, changes in vital signs, physical examination, 12-lead ECG parameters, hematology, and serum chemistry parameters.

Sample size

The sample size chosen for this trial was based on precedents set by similar ECG safety studies. From published trials, it is known that moxifloxacin induces a QTc prolongation of approximately 5 – 10 ms; the detectable difference between active treatment and placebo is usually defined as 5 ms. The standard deviation in the published moxifloxacin trials varied substantially and was approximately 12 – 13 ms on average. Replicate ECG measurements were planned for this trial, and this was expected to decrease the standard deviation to approximately 10 ms. Setting the significance level to $\alpha = 5\%$ (2-sided), and requiring a power of 80%, it was estimated that 64 evaluable subjects were needed per treatment group, resulting in a total of 256 subjects.

Pharmacokinetic analyses

Pharmacokinetic analyses were performed on the pharmacokinetic set, which included all randomized subjects who had received at least one dose of trial medication, had at least one pharmacokinetic measurement, and had no major protocol deviation that would have rendered the pharmacokinetic data unreliable. Analysis of variance with confidence intervals was performed for all pharmacokinetic endpoints except t_{max}, for which a nonparametric test was performed among subjects in the two fesoterodine treatment groups.

Results

Subjects

Subjects' baseline demographics were similar across groups (Table 1). Most subjects in each group were Hispanic, and the average age was approximately 53 years. Of the 261 subjects randomized to fesoterodine 4 mg (n = 64), fesoterodine 28 mg (n = 68), placebo (n = 65) or moxifloxacin (n = 64), 256 (98%) completed the trial. Two subjects in the fesoterodine 28-mg group discontinued because of adverse events; 2 subjects in the fesoterodine 28-mg group withdrew consent; and 1 subject in the placebo group discontinued, stating "other reasons."

Electrocardiographic parameters

At all time points during the trial, most subjects had normal findings for ECG parameters, and none of the abnormal findings were considered clinically relevant. Time-averaged by day and maximum changes from baseline in QTcF are shown in Table 2. There were no significant differences in the model-based adjusted mean change from baseline in QTcF on Days 1 or 3 between the fesoterodine 4-mg (–4.6 and –4.2, respectively) or fesoterodine 28-mg (–7.3 and –5.2, respectively) and placebo (–4.6 and –5.1, respectively) groups. The mean changes from baseline in QTcF after treatment with moxifloxacin (4.0 on Day 1 and 7.6 on Day 3) were significantly greater than those in the 3 other treatment groups on Days 1 and 3 ($p < 0.001$). The mean placebo-subtracted change from baseline in QTcF on Day 3 was approximately 10 ms (maximum) and 13 ms (time-averaged), and the lower limit of the 95%

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Table 1. Baseline demographics.

Characteristic	Placebo (n = 65)	FESO 4 mg (n = 64)	FESO 28 mg (n = 68)	Moxifloxacin (n = 64)
Age, y (mean ± SD)	53.1 ± 6.10	52.0 ± 5.35	53.6 ± 5.72	52.1 ± 5.60
Sex, n (%)				
Female	38 (58.5)	40 (62.5)	43 (63.2)	39 (60.9)
Race, n (%)				
White	1 (1.5)	1 (1.6)	4 (5.9)	2 (3.1)
Black	1 (1.5)	4 (6.3)	1 (1.5)	2 (3.1)
Hispanic	63 (96.9)	59 (92.2)	62 (91.2)	59 (92.2)
Latino	0	0	1 (1.5)	1 (1.6)
BMI, kg/m^2 (mean ± SD)	26.8 ± 2.86	26.7 ± 3.2	26.2 ± 3.06	27.0 ± 3.24

BMI = body mass index, FESO = fesoterodine, SD = standard deviation.

Table 2. Summary of time-averaged QTcF by day and maximum changes from baseline in QTcF.

Treatment	n	Endpoint LS mean	Comparison	Treatment difference	p value	95% CI
Day 1						
PBO	65	–4.6				
FESO 4 mg	64	–4.6	4 mg vs. PBO	0.0	0.978	–2.3, 2.4
FESO 28 mg	68	–7.3	28 mg vs. PBO	–2.7	0.022	–5.0, –0.4
MOXI	64	4.0	MOXI vs. PBO	8.6	< 0.001	6.3, 11.0
Day 3						
PBO	64	–5.1				
FESO 4 mg	64	–4.2	4 mg vs. PBO	0.8	0.452	–1.3, 3.0
FESO 28 mg	64	–5.2	28 mg vs. PBO	–0.1	0.895	–2.3, 2.0
MOXI	64	7.6	MOXI vs. PBO	12.7	< 0.001	10.6, 14.8
Maximum						
PBO	65	21.1				
FESO 4 mg	64	20.5	4 mg vs. PBO	–0.5	0.749	–3.8, 2.8
FESO 28 mg	68	18.5	28 mg vs. PBO	–2.5	0.124	–5.8, 0.7
MOXI	64	31.3	MOXI vs. PBO	10.2	< 0.001	6.9, 13.5

CI = confidence interval, FESO = fesoterodine, LS = least squares, MOXI = moxifloxacin, PBO = placebo.

confidence interval exceeded 5 ms, confirming the sensitivity of the study to detect a mean change of approximately 5 ms.

The model-based adjusted mean placebo-subtracted change from baseline in QTcF was close to 0 ms, and the upper limit of 95% confidence interval was well below 10 ms for both the therapeutic and supratherapeutic doses of fesoterodine. Similar results were observed for QTcI (Table 3). Results of the time-averaged ECG parameters showed no notable differences between treatment groups in the absolute values and model-based adjusted mean changes from baseline on Day 1 or Day 3 in the PR interval or the QRS duration.

Overall, there was a negative model-based adjusted mean time-matched change from baseline QTcF following dosing with either fesoterodine dose on Days 1 and 3 (Figure 2).

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Table 3. Summary of time-averaged QTcI by day and maximum change from baseline.

Treatment	n	Endpoint LS mean	Comparison	Treatment difference	p value	95% CI
Day 1						
PBO	65	–4.4				
FESO 4 mg	64	–5.6	4 mg vs. PBO	–1.1	0.485	–4.4, 2.1
FESO 28 mg	68	–9.5	28 mg vs. PBO	–5.0	0.002	–8.2, –1.8
MOXI	64	3.7	MOXI vs. PBO	8.1	< 0.001	4.9, 11.4
Day 3						
PBO	64	–5.2				
FESO 4 mg	64	–5.5	4 mg vs. PBO	–0.2	0.875	–3.3, 2.8
FESO 28 mg	64	–7.3	28 mg vs. PBO	–2.1	0.175	–5.1, 0.9
MOXI	64	7.2	MOXI vs. PBO	12.5	< 0.001	9.4, 15.5
Maximum						
PBO	65	20.7				
FESO 4 mg	64	20.1	4 mg vs. PBO	–0.5	0.809	–4.9, 3.8
FESO 28 mg	68	17.6	28 mg vs. PBO	–3.1	0.159	–7.3, 1.2
MOXI	64	31.0	MOXI vs. PBO	10.4	< 0.001	6.0, 14.7

CI = confidence interval, FESO = fesoterodine, LS = least squares, MOXI = moxifloxacin, PBO = placebo.

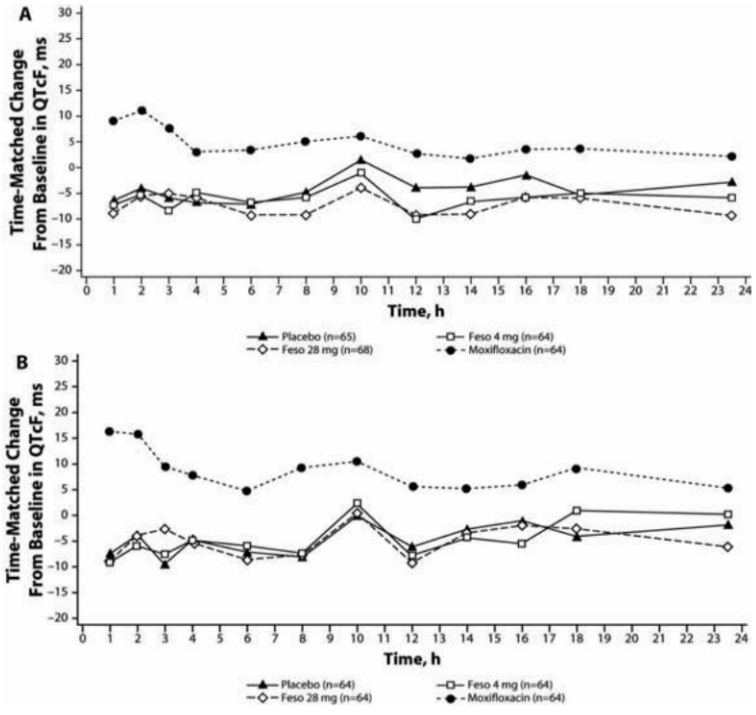

Figure 2. Time-matched change from baseline in QTcF on (A) Day 1 and (B) Day 3. Feso = fesoterodine.

Similar results were observed for QTcI. The magnitude of the decrease seen following treatment with fesoterodine was comparable with placebo treatment. Assay sensitivity was shown by an increase from baseline in QTcF following treatment with moxifloxacin.

Results of the subjects with a new onset QT or QTc outlier value were consistent with the absence of any QT prolongation effect associated with fesoterodine treatment (Table 4). No notable differences were seen in the number of QTcF outliers between placebo and either of the fesoterodine treatment groups. In contrast, there was a higher incidence of QTcF outliers following treatment with moxifloxacin. No subject had a new onset QTcF value > 480 ms. The percentages of subjects with new onset values for QTcF of > 450 ms were 4.6% (placebo), 3.1% (fesoterodine 4 mg), 0% (fesoterodine 28 mg), and 10.9% (moxifloxacin). The new onset values in QTcF that were > 450 ms in the fesoterodine 4-mg group represented one occurrence each in 2 subjects. One subject in the moxifloxacin treatment group had a change from baseline of ≥ 60 ms in the QTcF interval at Day 3; no other subject had a change from baseline in QTcF that was ≥ 60 ms at any time point during the trial. The percentage of subjects with increases in QTcF that were 30 – 60 ms was higher in the moxifloxacin group (50%) compared with the placebo (15.4%),

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Table 4. Summary of subjects with new onset QTc outlier values.

	Number of subjects (%)			
QTcF	Placebo (n = 65)	FESO 4 mg (n = 64)	FESO 28 mg (n = 68)	MOXI (n = 64)
> 450 ms	3 (4.6)	2 (3.1)	0	7 (10.9)
> 480 ms	0	0	0	0
> 500 ms	0	0	0	0
Increase of 30 to < 60 ms Increase of ≥ 60 ms	10 (15.4) 0	12 (18.8) 0	12 (17.6) 0	32 (50.0) 1 (1.6)
QTcI				
> 450 ms	4 (6.2)	5 (7.8)	2 (2.9)	8 (12.5)
> 480 ms	2 (3.1)	1 (1.6)	0	0
> 500 ms	0	0	0	0
Increase of 30 to < 60 ms Increase of ≥ 60 ms	7 (10.8) 0	8 (12.5) 1 (1.6)	11 (16.2) 1 (1.5)	31 (48.4) 1 (1.6)

FESO = fesoterodine, MOXI = moxifloxacin.

Table 5. Summary statistics of pharmacokinetic parameters of 5-HMT.

		Fesoterodine 4 mg		Fesoterodine 28 mg	
		Day 1 (n = 64)	Day 3 (n = 64)	Day 1 (n = 67)	Day 3 (n = 64)
Parameter	Unit	Mean (CV)			
AUC_{0-t}	ng × h/ml	24.4 (41.3)	28.6 (38.0)	212.4 (40.8)	242.5 (44.6)
C_{max}	ng/ml	2.38 (38.1)	2.66 (33.3)	18.1 (40.9)	20.7 (40.0)
t_{max}	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)

AUC_{0-t} = area under the concentration vs. time curve from time 0 to time of last measurable concentration, CL/F = apparent oral clearance, C_{max} = maximum plasma concentration, CV = coefficient of variation, t_{max} = time to reach C_{max}.

fesoterodine 4-mg (18.8%), and fesoterodine 28-mg (17.6%) groups.

Pharmacokinetic parameters

The values for the pharmacokinetic parameters C_{max} and AUC_{0-t} show the expected increase when comparing Day 1 and Day 3 data for each dose level (Table 5). Based on visual examination of the plots of 5-HMT trough concentrations on Days 1, 2 and 3, and consistent with the terminal half life of about 8 hours [8], it was apparent that steady state was achieved on Day 3. A 7-fold increase in the dose (from 4 to 28 mg) resulted in a similar 7-fold increase in the pharmacokinetic parameters C_{max} and AUC_{0-t}, which is consistent with dose-proportional pharmacokinetics of fesoterodine.

The relationship between model-based adjusted mean change in QTcF and mean plasma concentration of 5-HMT on Day 3 is shown for fesoterodine 4 mg (Figure 3A) and 28 mg (Figure 3B). The plasma concentration of 5-HMT shows the expected pharmacokinetic profile change over time, whereas the change in QTcF over time is relatively stable, suggesting that there is no correlation between the QTcF interval and plasma concentration of 5-HMT. Similar findings were observed between QTcI values and 5-HMT plasma concentrations.

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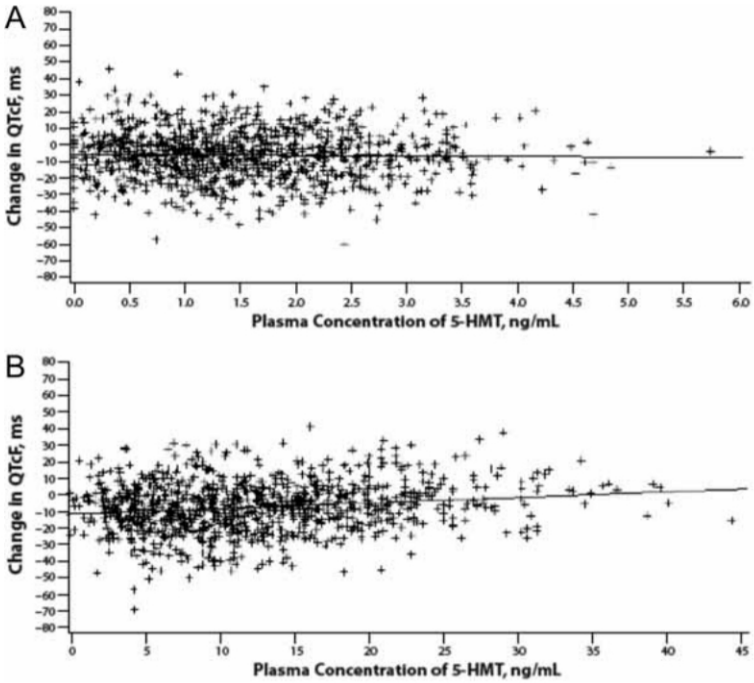

Figure 3. Correlation between change in QTcF and plasma concentration of 5-hydroxymethyl tolterodine (5-HMT) with (A) fesoterodine 4 mg and (B) fesoterodine 28 mg on Day 3. Data represent the pharmacodynamic and pharmacokinetic sets.

Safety

Fesoterodine was well tolerated. Subjects receiving fesoterodine 28 mg recorded a greater frequency of treatment-emergent treatment-related adverse events than did subjects receiving fesoterodine 4 mg, placebo, or moxifloxacin, respectively, including abdominal pain (7.4% vs. 0% vs. 0% vs. 0%), constipation (5.9% vs. 0% vs. 0% vs. 0%), dry mouth (4.4% vs. 0% vs. 0% vs. 0%), vomiting (4.4% vs. 0% vs. 0% vs. 1.6%), urinary retention (4.4% vs. 0% vs. 0% vs. 0%), and pharyngitis (1.5% vs. 0% vs. 0% vs. 0%) but not headache (5.9% vs. 6.3% vs. 6.2% vs. 4.7%). Adverse events experienced by subjects in the fesoterodine treatment groups, except for one case of conjunctival hemorrhage, were consistent with those seen in other trials and were expected for an antimuscarinic drug.

Two subjects, both in the fesoterodine 28-mg group, withdrew from the trial because of treatment-emergent adverse events. A 65-year-old woman discontinued because of dry mouth and pharyngitis reported on Day 1. Both events were mild in intensity; dry mouth was judged by the investigator to be possibly related to trial medication, and pharyngitis was judged by the investigator to be not related to trial medication. Both events resolved in 5 days. A 59-year-old man withdrew from the trial because of urinary retention requiring catheterization reported on Day 1. The event was severe and judged by the investigator to be probably related to trial medication. The event resolved in 3 days.

There were no abnormal clinical laboratory findings or changes in vital signs that were determined to be clinically significant in this subject population. No clinically important changes from baseline were apparent at any time point for systolic or diastolic blood pressure. The mean placebo-corrected increase in heart rate associated with a dosage of 4 mg/day and 28 mg/day of fesoterodine was 3 bpm and 11 bpm, respectively.

Discussion

This trial demonstrated that fesoterodine does not affect the QTc interval in healthy subjects aged 45 – 65 years after a therapeutic (4 mg) or a supratherapeutic dose (28 mg) of fesoterodine. The ICH-E14 guidelines dictate that negative thorough QT studies should demonstrate that the mean threshold for QT/QTc prolongation remain less than 5 ms and the upper bound of the 95% 1-sided confidence interval for the largest time-matched mean effect on QT exclude 10 ms. This was the case for fesoterodine. The time-matched results and time-averaged changes in QTcF interval from baseline, the primary endpoint, did not show an increase following fesoterodine 4 and 28 mg doses relative to placebo. This was also observed with the QTcI values; there were no significant differences between the fesoterodine treatment groups and placebo. No correlation was evident between 5-HMT plasma levels and the corrected QTcF interval as a marker for myocardial repolarization. The results observed with moxifloxacin were consistent with those in previous studies using moxifloxacin as a positive control [11] and confirm the sensitivity of this study to determine QT effects.

According to the ICH-E14 regulatory guidance [3], applying the most accurate correction factor available is important in a thorough QT study. Considering that QTcB overcorrects at

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elevated heart rates and undercorrects at heart rates < 60 bpm, it is not an ideal correction factor [6]. The QTcI is considered suitable for a thorough QT/QTc study. In this trial, the primary analysis was based on the QTcF because it is more accurate than QTcB in subjects with altered heart rate following treatment with antimuscarinic drugs [3].

The safety profile in this population of healthy volunteers was consistent with other Phase I, II, and III trials [1, 2, 10]. Adverse events (dry mouth and headache) were observed more frequently after administration of fesoterodine 28 mg. In this population of healthy adult volunteers, changes in vital signs were not considered clinically relevant. As expected, there was a modest dose-related increase in heart rate on Days 1 and 3 for both the fesoterodine 4-mg and 28-mg treatment groups, and the effect was more pronounced with fesoterodine 28 mg; the ability to increase heart rate is a known effect of antimuscarinic drugs.

In conclusion, there was no evidence of an association between fesoterodine, at either a therapeutic or supratherapeutic dose, and QTc prolongation or other ECG abnormalities. Steady-state levels of 5-HMT were reached with minimal accumulation after 3 days of dosing; exposure to 5-HMT was proportional to the dose of fesoterodine administered. The QTc interval prolongation was documented as expected with the positive control, moxifloxacin, confirming the study sensitivity. The therapeutic dosage of fesoterodine (4 mg/day) was safe and well tolerated after administration over 3 days in healthy male and female subjects aged 45 – 65 years.

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Conflict of interest

Bimal Malhotra and Kuan Gandelman are employees of Pfizer Inc, New York, NY, USA. Nolan Wood was an employee of Pfizer Inc, Sandwich, Kent, UK, at the time this study was conducted. Richard Sachse is an employee of Schwarz BioSciences, Monheim, Germany.

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