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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Toviaz®/ Fesoterodine Fumarate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00806494

PROTOCOL NO.: A0221058

PROTOCOL TITLE: A 12 Week, Multicentre, Open Label Study to Evaluate the Efficacy, Tolerability and Safety of a Fesoterodine Flexible Dose Regimen in Patients with Overactive Bladder

Study Centers: The study was conducted at 39 centers in the United Kingdom.

Study Initiation Date and Completion Dates: 07 February 2009 to 14 January 2010

Phase of Development: Phase 4

Study Objectives: The primary objective was to demonstrate the efficacy, in terms of reduction of micturitions, of 12 weeks flexible dose fesoterodine in subjects with overactive bladder (OAB) compared with baseline.

The secondary objectives were to assess the use of flexible dosing of fesoterodine on other bladder diary variables after 4 and 12 weeks compared to baseline, the effect of flexible dose fesoterodine on treatment satisfaction and health related quality of life (QoL) measures at 12 weeks compared to baseline, and the safety and tolerability of flexible dose fesoterodine in subjects with OAB.

The exploratory objectives were to analyze baseline data such as subject demographics, subject reported outcomes and bladder diary variables that could predict dose escalation after 4 weeks, understand the impact of cessation of fesoterodine after 12 weeks of therapy and to explore the potential impact of fesoterodine upon goal achievement after 12 weeks of therapy.

METHODS

Study Design: This was a single country, multi-center, open-label study which aimed to enter 326 male and female subjects with OAB symptoms from across the United Kingdom at approximately 41 centers in primary and secondary care sites, with each center enrolling

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approximately 8 subjects. The study required 5 in-clinic visits including the screening visit, baseline/enrollment visit, end of Week 4 visit, end of treatment visit (Week 12), and a post treatment visit (Week 16).

Number of Subjects (Planned and Analyzed): It was estimated that a sample size of 277 subjects would have been sufficient to provide 95% confidence intervals (CIs) of width no more than ±0.38 with 80% coverage probability. Allowing for a drop-out rate of 15%, a total of 326 subjects were required to be entered into the study.

All 331 subjects who were treated were included in the safety analysis set and were analyzed for adverse events (AEs). One subject was excluded from the full analysis set (FAS) because she did not have any post-baseline efficacy data for any efficacy endpoints. A total of 251 subjects (75.8%) were included in the per protocol analysis set (PPAS).

Diagnosis and Main Criteria for Inclusion: Eligible subjects were male or female outpatients ≥18 years old with OAB symptoms (subject-reported) for ≥3 months prior to screening/Visit 1 according to International Continence Society guidelines, mean urinary frequency of ≥8 micturitions per 24 hours as verified by the screening bladder diary prior to baseline/Visit 2, and mean number of urgency episodes ≥3 per 24 hours as verified by the screening bladder diary prior to baseline/Visit 2 (urgency episodes were defined as those with urinary sensation scale [USS] rating ≥3). Subjects with conditions that would contraindicate the usage of fesoterodine or could impact OAB symptoms, history of urinary tract surgery, active bladder stones and urinary tract infection were excluded from the study.

Study Treatment: All entered subjects were initially treated with fesoterodine 4 mg once daily for the first 4 weeks of treatment. At the end of Week 4, based upon a discussion between the subject and the investigator of efficacy and tolerability reported by the subject, the investigator could either increase the dose to 8 mg for those subjects who desired greater symptom improvement and reported good tolerability, or could continue the subject on the 4 mg dose, for the remaining 8 weeks of the study. No dose adjustments were allowed during the remaining 8 weeks of the treatment phase of the study. One tablet was to be taken with water at approximately the same time every day.

Efficacy Evaluations:

Bladder Diary:

Each subject was to complete a bladder diary for 3 consecutive days immediately preceding each clinic visit to record details of micturitions (frequency, urgency, urgency urinary incontinence [UUI]).

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Questionnaires:

Patient Perception of Bladder Condition (PPBC) is a self-administered, single-item, validated questionnaire that asked subjects to describe their perception of their bladder-related problems. The PPBC was administered at screening (Visit 1), baseline (Visit 2), Week 4 (Visit 3), Week 12 or early termination (Visit 4), and Week 16 (Visit 5).

Urgency Perception Scale (UPS; formerly referred to as Patient Perception of Urgency Scale) is a self-administered, single-item, validated questionnaire that measured the subject's perception of urinary urgency. It was administered at baseline (Visit 2), Week 4 (Visit 3), and Week 12 or early termination (Visit 4).

The Overactive Bladder-questionnaire (OAB-q) symptom bother scale consisting of 8 items asked the subjects how much they had been bothered by selected bladder symptoms during the past 4 weeks. It was administered at baseline (Visit 2), Week 4 (Visit 3), and Week 12 or early termination (Visit 4).

The King's Health Questionnaire (KHQ) is a self-administered questionnaire containing 21 questions that are scored in 9 domains (general health perception, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, severity of urinary symptoms). It was administered at baseline (Visit 2), Week 4 (Visit 3), and Week 12 or early termination (Visit 4).

The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) is a brief and comprehensive subject-completed questionnaire containing 6 items for the assessment and quantification of incontinence and its impact on QoL. It was administered at baseline (Visit 2) and at Week 12 or early termination (Visit 4).

The Benefit, Satisfaction and Willingness to continue (BSW) is a 3-item questionnaire designed to assess treatment benefit, subject satisfaction with treatment, and subject willingness to continue treatment. It was administered at Week 12 or early termination (Visit 4).

An initial version of the Self Assessment Goal Achievement (SAGA) questionnaire, before the final validated version was available, was included in the study as an exploratory endpoint. The SAGA questionnaire is a subject-completed, physician-reviewed tool to assess treatment goals and achievement of goals for subjects suffering from OAB and/or other urinary tract symptoms. SAGA First Assessment questionnaire was provided to the subjects at the end of screening visit, when the investigator took the time to explain the questionnaire. The second part (SAGA Follow-up questionnaire) was provided to the subjects along with their SAGA First Assessment finalized at baseline (Visit 2) (for reference).

The Treatment Satisfaction Question (TSQ) is a self-administered, 1-item measure of subject satisfaction for subjects receiving treatment for OAB. The TSQ was administered at the end of study at Week 12 or early termination visit (Visit 4) to assess subject's satisfaction with current treatment of fesoterodine.

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Safety Evaluations: AEs were monitored throughout the study. A urine dipstick test for red blood cells, white blood cells, glucose, protein, and nitrites was performed only at the screening visit for assessment of study entry qualification. A urine pregnancy test (beta-human chorionic gonadotropin) was done for women of child bearing potential at screening visit for assessment of study inclusion criteria and at Week 12 (end of treatment visit). Sitting blood pressure and pulse rate were recorded at all visits including screening, baseline, Week 4, and Week 12 or early termination visit.

Statistical Methods: All efficacy parameters were analyzed within the FAS. In addition, the primary efficacy endpoint was also analyzed using the PPAS.

The primary efficacy endpoint was the change in mean number of micturitions (micturition frequency [MF]) per 24 hours at Week 12 relative to baseline. The mean MF per 24 hours was calculated as the sum of all micturitions divided by the total number of diary days collected at that visit. The primary endpoint was summarized using descriptive statistics, which included the number of subjects, mean, standard deviation, minimum, median, maximum and 95% CI.

The secondary efficacy endpoints based on the bladder diary were:

- change in mean MF per 24 hours at Week 4 relative to baseline
- percent change in MF at Weeks 4 and 12 relative to baseline
- change and percent change in mean number of nocturnal micturitions (nocturnal micturition frequency [NMF]) per 24 hours at Weeks 4 and 12 relative to baseline in subjects with >0 episodes during the 3-day baseline diary period
- change and percent change in mean number of UUI episodes per 24 hours at Weeks 4 and 12 relative to baseline in subjects with >0 UUI episodes during the 3-day baseline diary period
- change and percent change in mean number of urgency episodes (urgency episode frequency [UEF]) per 24 hours at Weeks 4 and 12 relative to baseline
- change and percent change in mean number of nocturnal urgency episodes (nocturnal urgency episode frequency [NUEF]) per 24 hours at Weeks 4 and 12 relative to baseline in subjects with >0 episodes during the 3-day baseline diary period
- change and percent change in mean number of severe urgency episodes (severe urgency episode frequency [SUEF]) per 24 hours at Weeks 4 and 12 relative to baseline in subjects with >0 episodes during the 3-day baseline diary period
- change in mean number of incontinence pads used per 24 hours at Weeks 4 and 12 relative to baseline.

To support the interpretation of the primary analysis, a secondary analysis on the primary endpoint similar to the primary analysis was to be conducted based upon the PPAS. All

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other secondary diary endpoints (both absolute and percent change) were summarized as continuous endpoints with summary statistics provided for baseline and Weeks 4 and 12. These summary statistics were also provided for numeric and percentage changes from baseline to Weeks 4 and 12.

The secondary efficacy endpoints based on the questionnaires were:

- change in PPBC at Weeks 4 and 12 relative to baseline
- change in UPS at Weeks 4 and 12 relative to baseline
- change in OAB-q symptom bother and individual item (question) scores at Weeks 4 and 12 relative to baseline
- change in total score of each domain and individual item (question) score at Week 12 relative to baseline
- change in ICIQ-SF and individual item (questions 1-3) scores at Week 12 relative to baseline
- each BSW item and total score at Week 12
- percentage of subjects reporting satisfaction (including 'very satisfied' and 'somewhat satisfied') at Week 12.

The change from baseline to Weeks 4 and 12 in the PPBC were summarized. Frequency tables and change from baseline frequency tables were also presented. Frequency tables for the UPS categories at each visit and change from baseline to Week 4 and Week 12 frequency tables were presented. The change in the symptom severity/bother items and total of the OAB-q symptom bother scale at Week 4 and Week 12 relative to baseline was summarized. Absolute values and changes from baseline at Week 12 for each domain of the KHQ were summarized. The changes from baseline in item scores of the ICIQ-SF at Week 12 were summarized. Each item of the BSW and the total score at Week 12 were summarized. For the single item measure of satisfaction from the TSQ, the score (very dissatisfied to very satisfied) at Week 12 was summarized descriptively. In addition, the percentage of responders (ie, subjects who indicated being 'Very satisfied' or 'Somewhat satisfied') was summarized at Week 12.

Endpoints based on changes (absolute or percentage) from Week 12 (end of treatment) to Week 16 were evaluated for exploratory analyses.

The proportion of subjects escalating from fesoterodine 4 mg to fesoterodine 8 mg at Week 4 was summarized. Logistic regression analysis was used to explore the relationship between the final dose of fesoterodine (ie, whether subjects escalated to 8 mg or not) and screening/baseline factors, and other covariates, as follows:

- Baseline mean number of micturitions per 24 hours

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- Change in mean number of micturitions per 24 hours at Week 4 relative to baseline
- PPBC score at Week 4
- OAB_{wet} (at least 1 incontinence episode per 24 hours at baseline) vs OAB_{dry} (no incontinence episodes per 24 hours at baseline)
- Age
- Gender
- BMI
- Duration of OAB from the date of onset
- Presence/absence of anticholinergic AEs prior to Week 4

For the purposes of this analysis, the PPBC responses at Week 4 were categorized into 'no problems/some very minor problems', 'some minor problems', 'some moderate problems' and 'severe problems/many severe problems'. The reference category for comparing the proportion titrating for this factor was 'no problems/some very minor problems' and the odds of titrating for subjects in this category were compared to each of the other categories. The factors OAB_{wet} vs $OAB_{dry,}$ gender, presence/absence of anticholinergic AEs prior to Week 4 were modeled as binary endpoints, and baseline and change from baseline to Week 4 in mean number of micturitions per 24 hours, age, BMI and duration of OAB were modeled as continuous endpoints.

The covariate factors used in this analysis were summarized for all subjects, split by subjects who were dose titrated and not dose titrated at Week 4.

Safety data were summarized for all subjects included in the safety analysis set. All safety data were summarized and listed according to the sponsor's data standards.

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RESULTS

Subject Disposition and Demography: Table 1 summarizes the subject disposition. The most common reasons for discontinuations were 'other' reasons that were not related to study treatment (30 subjects [9.1%]) with the majority occurring during the post-treatment follow-up period between Week 12 and 16, and treatment-related AEs (25 subjects [7.6%]).

Table 1. Subject Disposition

Number of Subjects	Fesoterodine
Screened 418	
Assigned to study treatment	331
Treated	331
Completed	251 (75.8)
Discontinued	80 (24.2)
Related to study treatment	31 (9.4)
Adverse event	25 (7.6)
Lack of efficacy	6 (1.8)
Not related to study treatment	49 (14.8)
Adverse event	4 (1.2)
Lost to follow-up	10 (3.0)
Other	30 (9.1)
Subject no longer willing to participate in study	5 (1.5)

Subjects were mostly white (325 subjects [98.2%]) and female (263 subjects [79.5%]). Subjects had a mean age of 60.3 years (range: 23-86 years) and weight of 79.7 kg (range: 51.0-174.0 kg). All 331 subjects had a history of hypertonic bladder with a mean duration since onset of 7.7 years (range: 0.1 to 53.8 years).

Efficacy Results:

Primary Efficacy Results:

Results from this study showed a clinically relevant change (improvement) from baseline to Week 12 in the primary endpoint of mean MF per 24 hours. The mean change from baseline in the primary endpoint was -3.26 (95% CI: -3.62, -2.91) (Table 2).

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Table 2. Mean Micturition Frequency per 24 hours – FAS (LOCF)

	Fesoterodine N=330
Baseline	
n	330
Mean (SD)	12.82 (3.53)
Week 12	
n	317
Mean (SD)	9.58 (3.00)
Median (min, max)	9.3 (2.3, 23.3)
Change from Baseline at Week 12	
n	317
Mean (SD)	-3.26 (3.21)
Median (min, max)	-3.0 (-17.0, 7.7)
95% CI	-3.62, -2.91

FAS=full analysis set; LOCF=last observation carried forward; n=number of subjects; SD=standard deviation; min=minimum; max=maximum; CI=confidence interval; N=total number of subjects. Note: One subject was excluded from the FAS because she did not have any post-baseline data for any efficacy endpoints.

Secondary Efficacy Results:

At Week 12, there was a decrease from baseline (ie, improvement) in the NMF per 24 hours. The mean change from baseline to Week 12 was -0.78 (95% CI: -0.91, -0.64).

At Week 12, there was a decrease from baseline (ie, improvement) in the UUI (urinary sensation scale rating of 5) per 24 hours. The mean change from baseline to Week 12 was -1.64 (95% CI: -2.02, -1.25).

At Week 12, there was a clinically relevant decrease (improvement) from baseline in the UEF (urinary sensation scale rating ≥3) per 24 hours. The mean change from baseline to Week 12 was -5.10 (95% CI: -5.62, -4.58).

At Week 12, there was decrease from baseline (ie, improvement) in the NUEF (urinary sensation scale rating ≥3) per 24 hours. The mean change from baseline to Week 12 was -1.16 (95% CI: -1.32, -1.01).

At Week 12, there was a decrease from baseline (ie, improvement) in the SUEF (urinary sensation scale rating ≥4) per 24 hours. The mean change from baseline to Week 12 was -2.93 (95% CI: -3.36, -2.50).

At Week 12, the mean absolute change from baseline in the number of incontinence pads used per 24 hours was -0.64 per 24 hours (95% CI: -0.79, -0.49).

At baseline, all subjects (with responses at Week 12) considered their bladder condition caused them problems, with the majority (276 subjects [85.7%]) considering the problems moderate or severe, and 44 subjects (13.7%) considering the problems 'many severe'. At Week 12, 160 subjects (49.7%) had major improvements in bladder condition compared to baseline, and a further 94 subjects (29.2%) had minor improvements.

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At baseline, most subjects (with responses at Week 12) were not able to hold urine (81 subjects [25.2%]) or were able to hold urine until they reached a toilet but without finishing what they were doing (221 subjects [68.8%]). At Week 12, 154 subjects (48.0%) had improvements in UPS compared to baseline.

At Week 12, there was a decrease from baseline (ie, an indication of improvement) in the OAB-q Symptom Bother Score. The mean change from baseline to Week 12 was -37.25 (95% CI: -39.83, -34.66). Changes from baseline in scores for individual questions were comparable, no individual question score was markedly different.

At Week 12, there were decreases (ie, an indication of improvements) from baseline in all domains of the KHQ, with the greatest improvements for the Physical and Role Limitations domains. Changes from baseline in scores for individual questions were comparable, no individual question score was markedly different.

At Week 12, there was a decrease (ie, an indication of improvement) from baseline in the ICIQ-SF. The mean change from baseline to Week 12 was -5.13 (95% CI: -5.72, -4.54).

Mean changes from baseline in individual scores were negative for individual questions: frequency (Question 1) and amount (Question 2) of urine leak, and how much leaking interfered with life (Question 3).

At Week 12, >50% of subjects reported the maximum categories of benefit (Question 1: 'much benefit') and satisfaction (Question 2: 'very satisfied') from treatment. When subjects were asked to answer 'yes' or 'no' to whether they were satisfied (Question 3) and willing to continue treatment (Question 5), >75% of subjects answered 'yes' to each question. When the magnitude of subjects' willingness to continue was categorized, >60% reported the maximum category of 'very willing'.

The majority of subjects (73.6%) reported satisfaction with study treatment at Week 12.

Exploratory Results

At Week 16, for all micturition diary variables there were deteriorations (increases in frequency) from Week 12, ie, after the last dose of fesoterodine was taken.

Of 307 subjects, 195 subjects had a dose increase from fesoterodine 4 mg to fesoterodine 8 mg at Week 4. For 182 subjects the dose increase was due to insufficient clinical response and for 13 subjects the dose increase was for 'other' reasons. Most of the dose increases (111/195 subjects) were as result of the subject making the decision assisted by the investigator. Dose increases also occurred as a result of the subject (68 subjects) or investigator (12 subjects) making the decision, or due to 'other' reasons (4 subjects).

The stepwise logistic regression identified the covariates of change from baseline in micturition per 24 hours at Week 4 and response to the PPBC questionnaire at Week 4 as most strongly associated with whether a subject titrated or not. The other factors tested in the stepwise logistic regression (gender, age, BMI, presence or absence of anticholinergic AEs prior to Week 4, baseline mean number of micturitions per 24 hours, OAB_{wet}/OAB_{dry} and

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duration of OAB from the date of onset) were not found to be significant. Response to the PPBC Questionnaire at Week 4 gave different results for the sub-group that titrated to fesoterodine 8 mg compared to the sub-group that did not; eg, of the subjects who were titrated, 50 subjects (25.6%) had positive responses to 'My bladder condition causes me severe problems' compared to 1 (0.9%) of the subjects who were not titrated. Subjects who were titrated had more micturitions per 24 hours at Week 4 (mean=13.4; SD=3.75) than those who were not (mean=11.9; SD=2.98).

The most important goals at baseline, as identified by subjects in the SAGA questionnaire, were 'Reduce the sudden need to rush to the bathroom', 'Reduce frequency to the bathroom through the day' and 'Reduce frequency to the bathroom at night'. The most frequently achieved goals at Week 12 were 'Reduce difficulty starting or maintaining a urinary stream', 'Reduce frequency to the bathroom through the day' and 'Reduce my urine leakage'. Nearly 50% of subjects (49.5%) achieved the goal that was rated 'Most Important Goal', and 81.0% 'Somewhat achieved goals' or better.

Benefit of treatment with fesoterodine, was generally observed across all subjects for Fixed Total Score, Global Total Score, as well as OAB symptom-related Fixed Total Score and Global Total Score - derived from the SAGA questionnaire. The mean scores at Week 12 ranged between 47.62 and 48.63.

As per the TSQ, the majority of subjects reported satisfaction with the OAB medication (fesoterodine). There was a high correlation between the SAGA questionnaire (overall achievement of goals) and the TSQ.

Safety Results: An overview of AE experience during the study is provided in Table 3. A total of 605 AEs were reported by 254 subjects, and 295 AEs reported by 159 subjects were considered treatment-related. The most commonly reported all-causality AEs were dry mouth (99 subjects [29.9%]), constipation (30 subjects [9.1%]) and diarrhea (29 subjects [8.8%]) (Table 4). The majority of the most commonly reported AEs were considered treatment-related.

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Table 3. Overview of Treatment-Emergent Adverse Events - All-Causality and Treatment-Related

Number of Subjects	Fesoterodine (N=331)	
Subjects evaluable for AEs	331	
	All Causality	Treatment-Related
AEs	605	295
Number (%) of subjects:		
Subjects with AEs	254 (76.7)	159 (48.0)
Subjects with SAEs	11 (3.3)	3 (0.9)
Subjects with severe AEs	25 (7.6)	16 (4.8)
Subjects discontinued due to AEs	29 (8.8)	25 (7.6)
Subjects with dose reductions or temporary discontinuation due to AEs	14 (4.2)	4 (1.2)

Includes data up to 7 days after last dose of study treatment.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs are according to the investigator's assessment.
MedDRA (v12.1) coding dictionary applied.
N=number of subjects; AE=adverse event; SAE=serious adverse event; MedDRA=Medical Dictionary for Regulatory Activities

Table 4. Summary of Most Commonly Reported Treatment-Emergent Adverse Events (Occurring in >2% of Subjects) - All Causality and Treatment-Related

Number of Subjects with MedDRA v12.1 Preferred Term	Fesoterodine (N=331)	
	All Causality	Treatment-Related
Number (%) of subjects with AEs	254 (76.7)	159 (48.0)
Number (%) of subjects with:		
Dry mouth	99 (29.9)	97 (29.3)
Constipation	30 (9.1)	25 (7.6)
Diarrhea	29 (8.8)	19 (5.7)
Urinary tract infection	26 (7.9)	4 (1.2)
Headache	19 (5.7)	10 (3.0)
Dyspepsia	17 (5.1)	13 (3.9)
Nausea	15 (4.5)	9 (2.7)
Dizziness	11 (3.3)	6 (1.8)
Fatigue	9 (2.7)	6 (1.8)
Back pain	8 (2.4)	0
Dry eye	8 (2.4)	8 (2.4)
Cough	7 (2.1)	2 (0.6)
Dry throat	7 (2.1)	7 (2.1)

Subjects were counted only once per treatment in each row.
Includes data up to 7 days after last dose of study treatment.
MedDRA v12.1 coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities; N=total number of subjects; AE=adverse event

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Twenty-nine subjects (8.8%) experienced AEs that led to permanent study discontinuation; for 25 subjects (7.6%) these AEs were considered treatment-related. AEs leading to discontinuation that were experienced by more than 1 subject were dry mouth (10 subjects), dizziness (4 subjects), headache (3 subjects), nausea (3 subjects), constipation (2 subjects), pollakiuria (2 subjects), and dyspepsia (2 subjects).

Fourteen subjects (4.2%) experienced AEs that led to temporary study discontinuation or dose reduction; for 4 subjects (1.2%) AEs were considered treatment-related. AEs leading to temporary discontinuation or dose reduction that were experienced by more than 1 subject were diarrhea (4 subjects), dry mouth (2 subjects) and labyrinthitis (2 subjects).

One subject died post-study treatment. A 76-year-old male died post-study treatment due to a ruptured atheromatous aneurysm of the thoracic aorta, which was not considered treatment-related.

All serious AEs (SAEs) are listed by subject in Table 5. Eleven subjects (3.3%) experienced at least 1 treatment-emergent SAE, including 3 subjects (0.9%) who experienced SAEs considered treatment-related. All SAEs resolved by the end of the study with the exception of 1 SAE which was fatal.

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Table 5. Serious Adverse Events

Sex/Age (years)	Adverse Event	Start Day	Stop Day	Severity	Outcome	Investigator Causality/ Sponsor Causality
F/74	Hypertension	42	57	Severe	Resolved	Related/ Unrelated
	Edema peripheral	42	57	Moderate	Resolved	Unrelated/ Unrelated
F/52	Gastritis	23	30	Moderate	Resolved	Related/ Related
F/74	Femur fracture	45	51	Severe	Resolved	Unrelated/ Unrelated
	Fall	45	45	Severe	Resolved	Unrelated/ Unrelated
M/67	Left ventricular failure [a]	33	NA	NA	Resolving	Related/ Related
F/64	Transient ischemic attack	30	31	Mild	Resolved	Unrelated/ Unrelated
F/50	Diverticulitis	38	54	Severe	Resolved	Unrelated/ Unrelated
F/69	Myocardial infarction	3	>45	Severe	Resolving	Unrelated/ Unrelated
F/74	Diverticulitis	25	27	Severe	Resolved	Unrelated/ Unrelated
M/76	Aortic aneurysm rupture [a]	36	NA	NA	Fatal	Unrelated/ Unrelated
F/55	Edema peripheral	8	11	Moderate	Resolved	Unrelated/ Unrelated
F/38	Asthma [a]	78	101	Severe	Resolved	Unrelated/ Unrelated
M/77	Keratitis	19	30	Severe	Resolved	Unrelated/ Unrelated
	Angina pectoris	73	73	Severe	Resolved	Unrelated/ Unrelated
F/58	Chest discomfort	25	26	Severe	Resolved	Related/ Related
	Throat tightness	25	26	Severe	Resolved	Related/ Related
	Headache	25	26	Severe	Resolved	Related/ Related
	Palpitations	25	26	Severe	Resolved	Related/ Related
	Dyspnea	25	26	Moderate	Resolved	Related/ Related

Serious adverse event presentations were derived from a combination of data contained within the clinical study database and the corporate safety database. The corporate safety database was a separate, centralized, adverse event monitoring database that was continuously updated based on rapidly communicated reports from the investigators to the sponsor. The clinical study database was based on information provided from the CRFs/DCTs. Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.
F=female; M=male; NA=not available or not applicable
[a] Post-therapy.

Mean changes from baseline in sitting systolic blood pressure, sitting diastolic blood pressure, and sitting pulse rate were small. Nine subjects (2.8%) had an increase in sitting systolic blood pressure ≥30 mm Hg, and 7 subjects (2.1%) had an increase in sitting diastolic blood pressure ≥20 mm Hg. Five subjects experienced increased blood pressure during the study, which was reported as an AE; 1 subject experienced increased blood pressure that was reported as a treatment-related AE. There were no other safety concerns for vital signs.

CONCLUSIONS:

- The primary objective was to demonstrate the efficacy of 12 weeks flexible dose fesoterodine in subjects with OAB, in terms of a reduction from baseline in MF, and as a secondary objective, in terms of reductions in bladder diary variables (NMF, UUI, UEF, NUEF and SUEF). Results demonstrated that fesoterodine was efficacious in reducing MF and other bladder diary variables from baseline to Week 12.

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- The assessment of the effect of flexible dose fesoterodine on treatment satisfaction and health-related QoL measures at 12 weeks compared to baseline showed that the majority of subjects were satisfied with their treatment.

- A flexible dose regime of fesoterodine was safe and well tolerated. Overall, the safety data were consistent to those observed in prior fesoterodine studies and reported in the label for the OAB population:

    - The most commonly reported all-causality AEs were dry mouth, constipation and diarrhea; which are generally expected for this compound and population. There were no reported events of urinary retention.

    - Twenty-nine subjects (8.8%) experienced AEs that led to permanent study discontinuation; for 25 subjects (7.6%) AEs were considered treatment-related.

    - Eleven subjects (3.3%) experienced at least 1 treatment-emergent SAE, including 3 subjects who experienced treatment-related SAEs. All SAEs resolved by the end of the study with the exception of 1 SAE which was fatal.

- Exploratory analyses to understand the impact of cessation of fesoterodine after 12 weeks of therapy showed that for all micturition diary variables there were deteriorations (increases in frequency) after Week 12, ie, after the last dose of fesoterodine was taken.

- Exploratory analysis of dose titration data showed that the 2 factors that were most strongly associated with titration from fesoterodine 4 mg to fesoterodine 8 mg at Week 4 were change from baseline in MF and subject response to the PPBC questionnaire at Week 4.

- The exploratory SAGA questionnaire, used in this study to evaluate subjects' treatment goals with regard to their bladder problems, showed that 49.5% of subjects achieved the goal that was rated 'Most Important Goal', and 81.0% 'Somewhat achieved goals' or better.

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