1. SCIENTIFIC DISCUSSION

Introduction

Overactive bladder (OAB) syndrome is a common term used to describe a complex of lower urinary tract symptoms (LUTS). The symptoms include urinary urgency, with or without urge incontinence, usually accompanied by frequency and nocturia when appearing in the absence of pathologic or metabolic factors which would account for these symptoms[1, 2] Patients with an overactive bladder include those with and without a possible neurological cause for their symptoms.

Incontinence is not necessary for diagnosis; however is a chronic condition present in over half of female patients with OAB. Urinary incontinence is defined by the International Continence Society [1, 2] as the complaint of any involuntary leakage of urine.

The key symptom of OAB is urgency, the sudden compelling desire to void that is difficult to defer. Frequency is defined as the patient complaint of voiding too often by day, and nocturia is the complaint that the individual wakes at night to void. Urge incontinence is the involuntary loss of urine accompanied by or immediately preceded by urgency. [1, 2]

Other types of urinary incontinence include stress incontinence and mixed incontinence. Stress incontinence is the complaint of involuntary leakage of urine on effort or exertion or on sneezing or coughing. Mixed incontinence is the complaint of involuntary leakage associated with urgency and with exertion, effort, sneezing, or coughing. [1, 2]

Observations made during urodynamic testing do not represent a definite diagnose [1, 2]. The overactive bladder is a chronic condition defined urodynamically as detrussor overactivity, and characterised by involuntary bladder contractions during the filling phase of the micturition cycle.

The precise aetiology of overactive bladder is unknown. Neurologic illness or injury, bladder outlet obstruction, urethral weakness, detrussor hyperactivity, emergence of new voiding reflexes and idiopathic bladder overactivity are considered within the causes of OAB.

The prevalence of OAB has probably been underestimated because nearly all epidemiologic studies have been previously focused on urinary incontinence and because many patients are reluctant to discuss the subject with their doctors. Nevertheless, the recent standardisation of terminology by the International Continence Society (ICS) [1, 2] has facilitated obtaining reliable epidemiologic data on OAB. The overall prevalence in Europe has been estimated to be 16.6% on the basis of a population-based survey (15.6% for men and 17.4% for women)[3]. Although the overall prevalence is similar in men and women, there is a female-to-male preponderance in the prevalence of OAB with urge urinary incontinence, while OAB without urge urinary incontinence is more prevalent in men. Moreover, the prevalence of OAB symptomatology increased with advancing age in both men and women (41.9% of men and 31.3% of women over the age of 75 years) [3]. Finally, obesity is associated with symptoms of OAB, and the relationship between body mass index (BMI) and OAB with urge

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1 Sand P., Dmochowski P. Et al. Analysis of the standardisation of terminology of lower urinary tract dysfunction: report from the standardisation sub-committee of the international continence society.

2 Abrams P, Cardozo L, Fall M, et al: The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 21: 167-178, 2002.

3 Serels S. The Wet Patient: Understanding Patients With Overactive Bladder and Incontinence. Curr Med Res Opin 20(6):791-801, 2004.

4 Franklin M. Chu, et al. Pathophysiology of Overactive Bladder. The American Journal of Medicine (2006) Vol 119 (3A), 3S–8S.

5 Milsom P. How widespread are the symptoms o fan overactive bladder and how are they manager? A population based prevalence study. BJU International (2001), 87, 760-766.

urinary incontinence appears stronger than that between BMI and OAB without urge urinary incontinence[3].

The functional integrity of the lower urinary tract, the kidneys, and the nervous system (predominantly under the control of the parasympathetic nervous system) are the key factors to maintain continence and bladder function. Bladder function involves a bladder filling and urine storage phase, which leads to a bladder emptying phase. A stable bladder wall muscle (detrusor) and a functional sphincter allow bladder filling during the storage phase[4].

Undesired bladder muscle contraction may occur as the result of a break in the neurological pathway from the brain to the bladder. It can also occur if the bladder is irritated and the normal neurological impulses to inhibit urination are insufficient to keep the bladder relaxed as it fills.

The course of OAB is not life threatening, however symptoms may diminish the psychosocial, occupational, and sexual function of patients affecting quality of life. Patients consider urinary leakage, frequency and urgency to be bothersome[5]. Complications and comorbidities include urinary tract infection (UTI), skin ulceration in OAB with urge incontinence, and a greater risk of bone fracture from a fall, although some research has found little association. Sleep disturbances, restricted motility, isolation and depression are described as the psychological and lifestyle related consequences of OAB.

Treatment may be managed using nonpharmacologic and pharmacologic strategies.

Nonpharmacologic treatment:
Include lifestyle changes (controlled fluid intake), behavioural therapies, pelvic floor electrical stimulation, and surgical procedures.

Standard behavioural therapies include bladder training which focuses on voiding habits.

Pelvic muscle training exercises called Kegel exercises are primarily used to treat patients with stress incontinence.

Pharmacological treatment:
Medicinal products are aimed at diminish or suppress the intensity of involuntary detrusor contractions and include anticholinergic agents, antispasmodic medications, tricyclic antidepressants, and beta agonist.

With geographic differences, currently approved medical treatments are propiverine, propantheline, solifenacin, oxybutynin, tolterodine, flavoxate, darifenacine, imipramine, doxepin, terbutaline and trospium.

Oxybutynin and tolterodine are antispasmodic medications and are the most commonly used.

About the product

The claimed indication of fesoterodine 4 mg and 8 mg prolonged-release tablets was the treatment of overactive bladder with symptoms of urgency urinary incontinence and/or urgency and/or urinary frequency.

Fesoterodine (INN) is a new chemical entity developed as a hydrogen fumarate salt. Fesoterodine fumarate is the modified INN (INNM). It is the dextrorotary enantiomer of a derivative of 3,3-diphenylpropylamine with the chemical name "Isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4- (hydroxymethyl)phenyl ester hydrogen fumarate".

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[4] Franklin M. Chu, et al. Pathophysiology of Overactive Bladder. The American Journal of Medicine (2006) Vol 119 (3A), 3S–8S.
5 Milsom P. How widespread are the symptoms o fan overactive bladder and how are they manager? A population based prevalence study. BJU International (2001), 87, 760-766.

Fesoterodine is a competitive muscarinic receptor antagonist.

Type of application and other comments

The application submitted was in accordance with Article 8.3(i) of Directive 2001/83/EC, as amended.

No formal scientific advice was given by the CHMP.

2. Quality Aspects

Introduction

TOVIAZ is presented as prolonged-release tablets containing 4 mg and 8 mg of fesoterodine fumarate as active substance (corresponding to 3.1 mg and 6.2 mg fesoterodine respectively). The other ingredients are xylitol, lactose monohydrate, microcrystalline cellulose, hypromellose, glycerol dibehenate and talc. The film-coat consists polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, soya lecithin and indigo camine aluminium lake.

The prolonged-release tablets are packaged in aluminium-aluminium blisters.

Drug Substance

The drug substance is presented as the fumarate salt. Fesoterodine fumarate is Isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl)phenyl ester hydrogen fumarate according to the IUPAC nomenclature.

Fesoterodine fumarate is a white to off-white powder. It is freely soluble in aqueous solvents, soluble in some polar protic organic solvents (such as ethanol, methanol, glacial acetic acid, 2-propanol, propylene glycol) and polar non protic solvents (such as acetone, DMF, DMSO, acetonitrile), slightly soluble in toluene and it is practically insoluble in heptane.

- **Manufacture**

Fesoterodine fumarate is synthesised in eight reactions steps with two solid isolations.
The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included.

Specifications for starting materials, reagents, and solvents have been provided. Adequate control of intermediates has been presented.

Structure elucidation has been performed by ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, mass spectroscopy, optical rotation and chiral capillary electrophoresis. The results of the elemental analysis are consistent with the proposed molecular formula. Unambiguous proof of structure was provided by X-ray crystallography.

- **Specification**

The active substance specifications include tests for appearance, particle size, identification (IR and HPLC), melting point, water content (Karl Fischer), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur. – the specification only refers to the current Ph. Eur.), residual solvents (GC), impurities (HPLC), chiral purity (Capillary electrophoresis), specific optical rotation (Polarimetry) and assay (HPLC).
The specifications attributes reflect all relevant quality attributes of the active substance. The analytical methods which were used in the routine controls were described and their validations are in accordance with the ICH Guidelines.

Impurities have been extensively described, classified as process related impurities and possible degradation products, and qualified. Impurity limits in the specification are justified by toxicology studies.

The residual solvents were satisfactorily controlled in the active substance. All batch analysis results comply with the specification and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term, accelerated and stress studies were completed according to ICH guidelines and demonstrated adequate stability of the active substance. It was confirmed that the active substance is very stable when exposed to a variety of stressed conditions such as, thermal, humidity, acid or alkaline conditions, oxidizing conditions and light exposure. The results of the long-term and accelerated studies support the retest period.

Drug Product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance and the excipients are sufficiently justified. The drug substance fesoterodine fumarate was developed with the objective of having a crystalline and stable substance, but the free base of the drug substance was not suitable for processing since it is an oily liquid and does not have crystalline properties. Therefore, the hydrogen fumarate salt was chosen as a drug substance which is a crystalline non-hygroscopic substance with relatively high melting point.

Fesoterodine tablets are formulated as a prolonged release formulation in order to provide a once daily dosage form. The formulation is a hydrogel matrix tablet based on hypromellose. Results of formulation and process development studies demonstrate that the tablet formulation and the manufacturing process are robust.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as wet granulation, drying, dry blending, compression and coating unit operations. Furthermore, the equipment used is commonly available in the pharmaceutical industry.
The major steps to prepare fesoterodine tablets are the wet granulation and drying processes for the manufacture of the granules, dry blending of granulate with remaining excipients, and the tablet compression process. The wet granulation process was optimized with regard to sieve size, amount of water and mixing time.

The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specification.

- **Product Specification**

The drug product specifications were established according the ICH guidelines and include the following tests: appearance, odour (sensory examination), size, identification (HPLC, UV), impurities (HPLC), water content (Karl Fischer), dissolution, assay (HPLC), uniformity of dosage unit and microbial limits (Ph. Eur.).

- **Stability of the Product**

The stability studies were conducted according to the current ICH guideline. Three production scale batches of each strength have been stored at long term, intermediate and accelerated conditions in the proposed market packaging.

One production batch per strength was stored under elevated temperature light exposure and humidity conditions for 3 months and at ICH conditions.

Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product is expected to have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were two minor unresolved quality issues which have no impact on the benefit/risk ratio of the medicinal product. The applicant gave a letter of undertaking and committed to resolve these as follow up measures after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction

All pivotal safety pharmacology and toxicology studies including the determination of plasma concentrations of fesoterodine and/or SPM 7605 were carried out in conformance with Good Laboratory Practice (GLP) standards with the exceptions of an in vitro follow-up electrophysiological study (sodium channel,) and the determination of the secondary metabolites in selected plasma samples.

Pharmacology

- Primary pharmacodynamics

In vitro studies
Binding of fesoterodine and several of its in vivo metabolites to human recombinant muscarinic acetylcholine receptors (M1-M5) stably expressed in Chinese hamster ovary (CHO) cells was investigated in competition binding experiments. For comparison, tolterodine was used as the reference compound. SPM 7605, the primary in vivo metabolite, bound with high affinity to all the muscarinic receptors subtypes, see table below. There was no selectivity of SPM 7605 in binding to these receptors. Fesoterodine was also non-selective and had at least a 100-fold lower binding affinity than the active metabolite.

Binding to muscarinic receptor subtypes by fesoterodine, its metabolites and tolterodine

Muscarinic receptor	K_i (nmol/L)					
	Fesoterodine	SPM 7605	SPM 5509	SPM 6923	SPM 7833	Tolterodine
M_1	624	1.8	105	nd	40	3.0
M_2	562	1.7	97	nd	124	6.4
M_3	nd	6.3	489	nd	338	12
M_4	177	1.0	94	nd	35	1.9
M_5	nd	5.2	306	nd	96	4.6

Taking into account these results, the main active pharmacological principle of fesoterodine in vivo is SPM 7605.

In a separate study the binding affinity of tolterodine, fesoterodine and SPM 7605 to all human muscarinic receptor subtypes (M1-M5) was determined as shown in the table below.

Binding to muscarinic receptor subtypes by fesoterodine, SPM 7605 and tolterodine

Muscarinic receptor	Ki (nmol/L)		
	Fesoterodine	SPM 7605	Tolterodine
M_1	52	0.9	5.0
M_2	nd	2.9	14
M_3	209	1.7	4.6
M_4	23	1.1	4.6
M_5	285	2.7	7.2

Each determination was performed in duplicate
nd= not determined (50% binding at 1 micromol/L)

The data obtained in this study are qualitatively comparable to those presented previously. All three compounds showed no selectivity towards the 5 muscarinic receptor subtypes. SPM 7605 exhibited the highest affinity, while fesoterodine was much less potent. The difference in the absolute numbers measured in these studies in comparison to the study reported above may be explained by different cell clones and expression systems used by the two different laboratories, which performed the studies.

The specificity of fesoterodine and of its metabolite SPM 7605 was investigated in a broad screen of 41 receptors and ion channels. In particular, fesoterodine and its metabolite SPM 7605 do not interact with α-adrenergic, serotonergic, histaminergic, and excitatory amino acid receptors.

Functional antimuscarinic activity *in vitro* was demonstrated in organ bath studies with isolated bladder strips, where maximum inhibition of electrical field stimulation-induced contractions were observed at fesoterodine and SPM 7605 concentrations of 0.1 µM, tolterodine 0.3 µM, oxybutynin 0.1 µM and atropine 0.1 µM.

Both fesoterodine and the active metabolite SPM 7605 showed pronounced spasmolytic properties in the guinea-pig ileum model *in vitro* as can be expected from the anticholinergic mechanism of action.

In vivo studies
Intravenous administration of fesoterodine and SPM 7605 reduced micturition pressure and increased bladder capacity and intercontraction intervals at 0.01 mg/kg in the rat model (Breidenbach et al, 2002).

The effects of SPM 7605 on urinary bladder contractions and salivation were also investigated in cats (Nilvebrant et al, 1997). SPM 7605 dose-dependently inhibited acetylcholine-induced contractions of the bladder (ID50 5.1 µg/kg). There was also a dose-dependent inhibition of electrically stimulated salivation observed with an ID50 of 13.7 µg/kg. This indicates that SPM 7605 is three times more potent at the urinary bladder compared to the salivary gland.

- Secondary pharmacodynamics and Safety pharmacology

Cardiovascular system
The cardiovascular system has been extensively investigated both *in vitro* and *in vivo*.

In human embryonic kidney (HEK293) cells expressing hERG, fesoterodine and SPM 7605 induced a concentration-dependent inhibition of hERG current with IC_{50} values of 3.6 and 0.5 µM, respectively. The metabolite SPM 5509 showed a similar concentration-dependent inhibition of hERG current (IC_{50} = 3.3 µM) while the metabolite SPM 6923 had a weaker effect (inhibition of 22% at 300 µM, the highest concentration tested). In single Chinese hamster ovary cells expressing the human SCN5A gene, SPM 7605 concentration dependently reduced the fast sodium current.

Blockade of the hERG-mediated potassium current has also been observed for other antimuscarinic agents such as solifenacin (IC_{50}0.27 µmol/L), tolterodine (IC_{50}0.009 µmol/L) and darifenacin (IC_{50}0.077 µmol/L).

The effects of fesoterodine, SPM 7605 and tolterodine on cardiac ion channels are summarized in the following table.

Effects of fesoterodine, SPM 7605 and tolterodine on cardiac ion channels

Cardiac ion channel	IC50 (µmol/L) or % inhibition at 15 µmol/L		
	Fesoterodine	**SPM 7605**	**Tolterodine**
hERG	3.6	0.28 and 0.5	0.011
SCN5A	9.5-10.6	13.6-20.9	2.7-7.0
Ca, L-Type	44%	18%	17%

The cardiac electrophysiological studies were performed with fesoterodine and its metabolite SPM7605.
In vitro, a concentration-dependent increase in action potential duration was observed in isolated canine Purkinje fibres at 70% (APD70) and 90% (APD90) from $1.5x10^{-7}$ to $1.5x10^{-6}$ M. The increase was statistically significant at $1.5x10^{-6}$ M. At $1.5x10^{-5}$ M, APD50 and APD70 were decreased, associated with a decrease in the amplitude of action potential and in the depolarisation rate, suggesting an interaction with the sodium channel.

In vivo, a dose-dependent tachycardia with no change in mean arterial pressure was observed in rats dosed with fesoterodine 3-30 mg/kg as expected from the antimuscarinic effect of fesoterodine. Moreover, a dose-dependent decrease in baroreflex sensitivity was observed which might indicate that fesoterodine can induce orthostatic hypotension in man, however, this has not translated in to a clinical signal.

In vivo, in anaesthetised dogs, slight decreases (3 to 9%) in systolic blood pressure, pulmonary arterial pressure and renal artery blood flow were found at 8 µg/kg of intravenous fesoterodine.

At a dose of 800 µg/kg i.v., decreases in diastolic blood pressure, heart rate and coronary artery blood flow and prolongation of the QT interval and QTc interval were noted. However, in a 13-week toxicity study with continuous intravenous infusion of SPM7605 in dogs, no effect on the QT or QTc interval was observed at free plasma concentrations 21-33 fold higher than measured following 8 mg in humans. The clinical relevance of these findings for humans is not clear . (See clinical section)

Central nervous system
The main CNS-related effect of fesoterodine is a slight CNS stimulatory effect observed in mice (10-30 mg/kg p.o.) in behavioural tests. In accordance with the proposed mechanism of action, the increases in restlessness and spontaneous locomotor activity are expected. Fesoterodine (3-30 mg/kg) had a slight analgesic effect at 30 mg/kg but no pro-convulsive or anticonvulsive properties. A statistically significant decrease in body temperature was observed at 3 mg/kg at one time point only but not at 10 or 30 mg/kg and is considered of low clinical relevance.

Other organ systems
No relevant effects have been observed on respiratory, autonomic nervous, renal and gastro-intestinal systems.

- Pharmacodynamic drug interactions

The ability of fesoterodine to interact pharmacodynamically with other drugs has not been investigated. However, the mechanism of action of muscarinic receptor antagonist is well documented and potential pharmacodynamic drug interactions are published.

Pharmacokinetics

Absorption
After oral administration, fesoterodine is well absorbed but rapidly metabolized to SPM 7605, mainly in mice and rats. Tmax was approximately 0.5 h for mouse, rat and rabbit and 1 h in dogs.

Bioavailability was determined to be 50, 14 and 98% in mice, rats, and dogs, respectively. Due to a rapid hydrolysis of fesoterodine only SPM 7605, the major metabolite, was determined in mouse, rat, rabbit and human plasma. Fesoterodine is more slowly hydrolysed in dogs, where both fesoterodine and SPM 7605 can be detected in plasma. The extent of systemic exposure was characterized by non-linear (dose-dependent) kinetics with a more than dose-proportionate increase of fesoterodine in dogs and of SPM 7605 in mice and dogs.

The pharmacokinetic parameters C_{max} and AUC of fesoterodine and its metabolites, in the plasma of human subjects, and in mice and dogs at the NOAEL are compared below.

Table 9. Pharmacokinetic parameters of fesoterodine and its metabolites in human, mouse and dog plasma following oral administration of fesoterodine

Parameter	Species	Analyte				
		Fesoterodine	**SPM 7605**	**SPM 5509**	**SPM 7790**	**SPM 7789**
C_{max} (ng/mL)	**Man**	**nd**	**4.67 ± 2.02**	**13.4 ± 3.11**	**7.45 ± 2.36**	**0.29 ± 0.14**
	Mouse	nd	144 (male) 258 (female)	96.2 (male) 153 (female)	82.2 (male) 187 (female)	21.7 (male) 43.7 (female)
	Dog	3.27 4.18 4.96 38.3	24.91 108 9.67 45.5	271 914 185 369	113 244 98 115	6.44 25.1 3.58 10.8
AUC [a] (h·ng/mL)	**Man**	**nd**	**51.73 ± 13.85**	**205.1 ± 40.28**	**124.6 ± 39.26**	**2.18 ± 1.59**
	Mouse	nd	289 (male) 479 (female)	237 (male) 358 (female)	325 (male) 535 (female)	66.2 (male) 100 (female)
	Dog	7.36 4.56 25.9 78.0	101 219 55.6 269	2243 2111 2165 2974	1099 629 1272 1045	49.8 52.3 39.6 90.6

Data presented are after single oral administration of 8 mg fesoterodine in Phase 1 trial SP567 (arithmetic mean ± SD, n=11) and after repeated oral administration to mice (NOAEL=25 mg/kg/day, 6-month study) and dogs (NOAEL=2.5 mg/kg/day, 9-month study) as *individual* data.
nd - not detectable.
a - AUC(0-tz) in male human subjects, AUC_{last} in mice and dogs
SPM 7605=hydroxy metabolite, SPM 5509=carboxy metabolite, SPM 7790=carboxy-N-desisopropyl metabolite, SPM 7789=N-desisopropyl metabolite

Distribution
The distribution of [^{14}C] fesoterodine and/or its metabolites was studied in mice, rats and dogs following oral administration. Fesoterodine was widely distributed in mice and rats. Highest levels of radioactivity were found in organs involved in drug elimination; however no specific affinity/uptake to organs/tissues was detected. No notable accumulation was observed. In dogs, the radioactivity is less widely distributed with highest concentrations of radioactivity detected in the intestinal tract. A slight accumulation was observed in skin and eyes. [^{14}C] Fesoterodine and/or its metabolites crossed the blood-brain barrier to a low extent and did cross the placenta and distribute into fetal tissues in mice. The serum protein binding was low (21-30%) in mouse, rat and dog comparable to that in man (53%).

Metabolism

In vitro, fesoterodine is extensively metabolized by non-cytochrome P450 activity to the major metabolite SPM 7605 (human, rabbit > mouse > dog >> rat). Further metabolism takes place via CYP2D6 to the carboxy metabolite SPM 5509 (major) or via CYP3A4 to the N-desisopropyl metabolite SPM 7789 (minor). Both SPM 5509 and SPM 7789 are then further metabolized to SPM 7790.

In vivo, in all animal species (and humans), the major biotransformation pathways involved rapid hydrolysis that leads to the formation of SPM 7605 followed by oxidation and N-dealkylation (mediated both by CYP activity). In these species, fesoterodine cannot be detected in plasma and SPM 7605 can be regarded both as major metabolite and active principle of fesoterodine. No gender differences have been observed except in the rat. The dog does not hydrolyze fesoterodine to the same extent as observed in the other species, thus fesoterodine can be detected in plasma of the dog together with the other metabolites.

No or low inhibitory interactions with CYP1A2, 2C9, 2C19, 2D6 and 3A4 were detectable for fesoterodine.

Excretion
Fesoterodine and/or its metabolites are rapidly excreted with the majority of the dose recovered within 48 hours. In the dog, the majority of radioactivity (60-67%) was excreted in urine. Both urinary and fecal elimination are relevant in the mouse. In the rat, the largest portion of radioactivity was recovered in feces. In humans, about 70% of an oral dose of fesoterodine is recovered in urine.

Toxicology
The toxicity of single doses of fesoterodine has been investigated via the oral and i.v. routes of administration in the mouse and rat.

Repeated-dose toxicity studies have been conducted in mouse, rat and Beagle dog. Based on pharmacokinetic/metabolism data, the mouse and dog are considered the most relevant animal species for the human situation, the rat being less relevant due to different metabolism.

- Single dose toxicity

Dose-related clinical signs were mainly CNS related such as reduced motility, ataxia, dyspnoea and reduced muscle tone starting at 215 mg/kg (oral) or 21.5 mg/kg (iv). Approximate LD50 in the mouse was 316/31.6 mg/kg and in the rat 681 (males) 454 (females)/31.6 mg/kg

Toxicokinetic data are available from the acute toxicity studies using p.o. administration. The exposure in mice and rats at the non-lethal dose 215 mg/kg was respectively 80-300 times and 12-30 times the human exposure.

- Repeat dose toxicity (with toxicokinetics)

Fesoterodine was administered orally to mouse for 6 months, rats for 3 months and Beagle dogs for 9 months. Furthermore, mice were dosed via 4-hour/day intravenous infusion with fesoterodine 18 mg/kg for 14 days. Dogs were treated similarly with fesoterodine 6 mg/kg for 14 days (4-hour/day), and with SPM 7605 4.5 mg/kg for 13 weeks (24-hour/day). The main target organ of toxicity was the liver in rat. No target organ of toxicity was identified in the mouse or the dog.

Mice were dosed at 5, 25, and 75 mg/kg, the latter increased in week 16 at 125 mg/kg (females) and 100 mg/kg (males) of fesoterodine by oral gavage for 6 months. Some high dose animals died probably in relation to urinary tract infection secondary to bladder distension, an exaggerated pharmacodynamic (antimuscarinic) effect of fesoterodine/SPM 7605. High dose animals showed also piloerection and a slightly reduced body weight gain (5% in males and 8% in females), a slight reduction (20-24%) in platelets in both male and female and a slight increase in glucose (26%) in female only. Triglycerides were significantly reduced and plasma urea was increased in high dose male mice in week 13 and 26. These moderate changes, without corresponding findings in clinical

trials, are considered of low clinical relevance.

The NOAEL was 25 mg/kg at which Cmax was 144 ng/ml in males and 258 in females and AUC 379 h ng/ml in males and 575 h ng/ml in females. Thus based on Cmax the exposure margin to human exposure is 16-30 and 4-6 based on AUC values.

No additional toxicological effects were observed in studies of shorter duration or in a 14-days study with intravenous infusion where exposure did not exceed the exposure obtained in the high dose group dosed by oral gavage.

Rats were dosed with 5, 25 and 75 mg/kg fesoterodine by oral gavage (13 week MTD study). Body weight was reduced (3-11%) in high dose males while only a marginal effect was noted in females. The food consumption was decreased by approximately 10% in both males and females. A dose of 75 mg/kg resulted in increased bilirubin, cholesterol, ALAT, ASAT, ALP activity and triglycerides. Absolute and relative liver weights were significantly increased in females at 25 mg/kg and in both sexes of the high dose group. Histopathology showed a minimal to moderate pericholangitis with mild bile duct proliferation in high dose females. Thus, the target organ of toxicity is the liver in rats most pronounced in females.

In a supplementary study including toxicokinetics, at dosage of 5, 15 and 45 mg/kg, the NOAEL was determined to be 15 mg/kg.

At a dose of 15 mg/kg Cmax levels of 13.9-93.1 ng/ml has been observed in male rats and corresponding values for females is 6.8-36.8 ng/ml. AUC value for males is 125-182 h ng/ml and 47.2-73.4 h ng/ml in females. Exposure margins of 1-10 were obtained based on Cmax values and based on AUC values an exposure around clinical exposure was obtained in rats.

In the pivotal 9-month study *Beagle dogs* received fesoterodine 0.5, 2.5 and 12.5 mg/kg by oral capsule. The most pronounced clinical finding was related to the eyes: mydriasis conjunctivitis and adhered eyelids. The animals had to be treated with artificial lachrymal fluid from test day 29 onwards. These effects are related to the anticholinergic mechanism of action of fesoterodine/SPM 7605. Clinical biochemistry showed an increase in bilirubin and plasma urea levels. However, this was not associated with any drug-related macroscopic or histopathological changes of the liver.

The electrocardiographic evaluation demonstrated a dose-dependent (animals dosed with 2.5 and 12.5 mg/kg) increase in heart rate in male and female dogs estimated 4 hours after dosing. The effect had nearly subsided 24 hours after dosing and no effect on QRS, QT, QTc, PQ-intervals and P segment were observed. In addition no effect on blood pressure was noted.

The NOAEL was considered to be 2.5 mg/kg, all effects being considered as exaggerated pharmacodynamic effects of fesoterodine/SPM 7605.

- Genotoxicity

In vitro, fesoterodine has been tested in Ames test and in chromosomal aberration tests using metabolic activation both from rat and mouse liver. No induced mutation frequency or chromosomal aberrations were observed up to cytotoxic concentrations of fesoterodine either with or without metabolic activation.

In vivo, fesoterodine has been tested in the micronucleus test (bone marrow) in mice at a maximum oral dose of 250 mg/kg. No genotoxic effects were induced. Toxicokinetic data were not estimated in this study, however based on data from other toxicity studies an adequate exposure level of the animals has been reached.

- Carcinogenicity

Two 104 weeks carcinogenicity studies have been performed in mice and rats. In the *mice* study,

groups of 50 males and 50 females received 5, 15, and 45 mg/kg by oral gavage. The 45 mg/kg dose did not result in sufficient degree of toxicity and the dose was increased to 60 mg/kg but was later reduced to 45 and 30 mg/kg in males due to high mortality rates. The survival rate was 32% in high dosed males and 38% in females. A tightly filled intestine and rectum was noted in all dosage groups related to the anticholinerigic mechanism of action of fesoterodine/SPM 7605. No difference in neoplastic lesions was observed between animals on active treatment compared to placebo.

In *rats* groups of 50 males and 50 females/group were treated with 5, 15, and 45 mg/kg by oral gavage. The 45 mg/kg dose did not result in sufficient degree of toxicity thus the dose was increased to 60 mg/kg. No difference in neoplastic lesions was observed between animals on active treatment compared to placebo. At histopathology, tightly filled urinary bladder and minimal to moderately reduced secretory activity in salivary glands and lacrimal glands were noted. These effects are related to the pharmacodynamic mechanism of action.

The exposure to SPM 7605 at the high dose level was Cmax 340.68 ng/ml and AUC 1406.3 h ng/ml in males and Cmax 286.40 ng/ml and AUC 740.7 h ng/ml in females. Thus, exposure margins of 7-14 based on AUC and 33-39 based on Cmax are obtained.

In conclusion, fesoterodine was not carcinogenic in mice and rats.

- Reproduction Toxicity

Fertility and early embryonic development
In male mice, no effects on clinical signs, body weight gain or male fertility parameters (sperm number, motility and viability, weight of testis and epididymis) were observed up to maximum dose of fesoterodine 45 mg/kg.

Female mice dosed with 45 mg/kg showed a marginal reduction in body weight probably caused by the reduced number of fetuses. The number of corpora lutea, implantation sites and viable fetuses was slightly but significantly reduced. The uterine weight was slightly but significantly decreased correlated with the reduced number of fetuses. Fesoterodine had no effect on resorption rate, preimplantation and post-implantation loss. The NOEL for fertility was 15 mg/kg which corresponds to a Cmax value of 43.4-77.3 ng/ml resulting in exposure margins of 5-9 times the human exposure.

Embryo-fetal development
In *mice*, dams at the high dose level (75 mg/kg) showed a decrease in body weight which was caused by the increased resorption rate. No maternal toxicity was seen. Embryotoxicity was observed evident as a slight but statistically significant reduction in body weight for male fetuses at 45 mg/kg; at 75 mg/kg for both male and female fetuses. Furthermore, at 75 mg/kg an increase in the number of total resorptions was observed. The mean post-implantation loss was 16.6%; and complete in one female. Accordingly, the number of live fetuses was decreased. Four malformed fetuses were noted, three with cleft palate in each of the dosage groups (15, 45 and 75 mg/mg). One 45 mg/kg fetus had exencephaly. The NOEL was 15 mg/kg which corresponds to a Cmax value of 79.7 ng/ml resulting in an exposure margin of 9 times the human exposure.

In *rabbits*, no maternal toxicity (net body weight gain or decreased food consumption) was seen following oral gavage administration of fesoterodine. In the high dose group (27 mg/kg p.o.) the post-implantation loss was slightly (+17.1%) increased and the number of resorptions was threefold increased. One high dose dam had complete post-implantation loss early during gestation. Seven malformed fetuses, uni- or bilateral hyperflexion of the fore and/or hind paws and/or crossed legs were noted in three controls, two 3 mg/kg and two 27 mg/kg fetuses. These changes were considered to be within the normal range. At 27 mg/kg, a statistically significant increased incidence of retarded ossification of the sternebra(e) and total retardations was noted. The NOEL was 9 mg/kg which corresponds to a Cmax value of 57.3 ng/ml resulting in an exposure margin of 6 times the human exposure.

A study in rabbits using subcutaneous bolus injection of fesoterodine 0.5, 1.5 and 4.5 mg/kg which enabled a high exposure did not demonstrate any embryotoxic or teratogenic effects. Severe maternal toxicity was observed at the high dose level while only slight maternal toxicity was observed with administration via oral gavage up to a dose of 27 mg/kg.

Prenatal and postnatal development, including maternal function
The peri- and postnatal toxicity was investigated in the *mouse* at dose levels of 10, 30 and 60 mg/kg. Evidence of maternal toxicity of the F_0–dams was noted at the high dose level as slightly decreased body weight from gestation day 10 onwards which did correlate with the reduced number of fetuses. A decreased body weight gain was noted at the end of lactation weeks 1 and 2 (-11% and -10%). Similar effects were observed on food consumption. Slight effects on reproduction, not statistically significant were noted at the 30 and 60 mg/kg dose levels; slightly reduced number of implantations and slightly reduced number of pups alive at 60 mg/kg. A dose-dependent decrease in lactation and overall survival indices were observed from 30 mg/kg, in addition also decrease in viability at 60 mg/kg. The mean body weights of the pups were marginally decreased. No treatment related changes were noted at necropsy of the animals.

In the F_1-generation, ear-opening was marginally delayed at 30 and 60 mg/kg and consequently also a decreased response to auditory startle reflex by 31.5% and 46.3%, respectively. No adverse effects were noted on F_1-dams and male F_1-partners or on the F_2-generation until weaning. The NOEL for F_0 and F_1 is 10 mg/kg and the NOAEL for F_2 is higher than 60 mg/kg resulting in an exposure margin of approximately 6.

In conclusion, reproduction studies have shown minor embryo-toxicity (increased number of resorption, pre-implantation and post-implementation losses). This is mentioned in the SPC.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
The absence of studies on juvenile animals is accepted considering the proposed indication for fesoterodine.

- Toxicokinetic data

The applicant has conducted a number of toxicokinetic studies, where the plasma exposure to fesoterodine at the maximum therapeutic dose (8 mg, 0.11 mg/kg) has been compared to reference doses in animal studies.

For exposure comparisons animal versus human, the following human data were used, AUC of 98.3 h ng/ml and Cmax of 8.62 ng/ml (observed in healthy male volunteers receiving the maximum recommended dose of fesoterodine 8 mg, fed status, poor CYP2D6 metabolizers).

Table. SPM 7605 exposure in mouse after repeated oral administration of fesoterodine for 6 months (LPT 13348/00). All parameters are from the end of the dosing period.

Dose (mg/kg/day)	**C_{max} (ng/ml)**		**$AUC_{(0\text{-}24\ hr)}$ (h*ng/mL)**		**C_{trough} (=C_{24h}) (µmol/L)**	
	Male	Female	Male	Female	Male	Female
5	14.0	14.7	28	29	0.00	0.00
25	144	258	379	575	0.00	0.00
75 (100/125)	1670	2970	3806	8325	3.15	1.87

Table 17. SPM 7605 exposure in dog after repeated oral administration of fesoterodine for 9 months (study LPT 13349/00 n=5/sex).

Dose (mg/kg)	**C_{max} (ng/mL)**		$T_{max\ (h)}$		**$AUC_{(0\text{-}24\ h)}$ (h*ng/mL)**	
	M	F	M	F	M	F
0.5 mg/kg	2.65 (1.59-3.27)	1.79 (0.72-3.78)	1 (1-2)	1 (1-2)	5.43 (4.15-6.78)	3.05 (1.60-6.42)
2.5 mg/kg	54.2 (24.9-108)	36.0 (9.25-105)	1 (1-2)	2 (1-4)	114 (107-237)	92.9 (75.0-267)
12.5 mg/kg	763 (558-876)	674 (246-1739)	2 (1-4)	1 [i] (1-2)	3484 (1907-4118)	2679 (2040-5386)

The safety margins established comparing SPM 7605 AUC values show that in chronic toxicity studies the average systemic exposure was at least 1.5 (dog, iv) or 3.9-fold (mouse) higher as compared to man. In carcinogenicity studies was at least 7.7- (mouse) or 7.5-fold (rat) higher in terms of AUC at the highest dose as compared to man.

In embryo-foetal development studies, the systemic exposure to SPM 7605 at NOEL (mouse)/NOAEL (rabbit) was at least 0.9- (mouse) or 1.3-fold (rabbit, sc) in terms of AUC at the highest dose. In these toxicity studies, doses of fesoterodine which caused no toxicological consequences (NOAEL), were similar to the highest therapeutic dose of fesoterodine. Therefore, the occurrence of the above animal findings in humans cannot be ruled out. This is appropriately reflected in the SPC.

- Local tolerance

The potential of fesoterodine and its metabolite SPM 7605, to produce skin irritation was studied in rabbits

.
In the patch test a very slight erythema and edema were noted. Fesoterodine is classified as irritating to eyes.

- Other toxicity studies

Antigenicity
Fesoterodine did not provoke skin sensitization reactions in guinea pigs.

Biocompatibility
Fesoterodine and SPM 7605 were studied for their biocompatibility and haemolytic properties on human blood. Neither fesoterodine nor SPM 7605 showed any influence on the parameters observed.

Immunotoxicity
The Plaque Forming Colony test has shown that fesoterodine 5-75 mg/kg p.o. for 28 days has no immuno-toxicological properties in mice with respect to an antibody response to IgM and IgG.

Phototoxicity
According to guideline, photosafety testing of fesoterodine is justified.. SPM 7605 revealed no phototoxic potential under the present test conditions.

Ecotoxicity/environmental risk assessment

As per the guideline, a Phase I estimation of exposure based on the fesoterodine fumarate maximum daily dose of 8 mg and the default Fpen value of 0.01, results in a PECsurfacewater =0.04 µg/L, which is > the Action limit of 0.01 µg/L.

Therefore, a Phase II assessment is currently underway and will be submitted as a post-approval commitment, 2Q07.

We propose deleting the complete table above

Discussion on the non-clinical aspects

Fesoterodine is a competitive, specific and non-selective muscarinic receptor antagonist. It is rapidly and extensively hydrolysed by non-specific plasma esterases to the 5-hydroxymethyl derivative (SPM 7605) its primary active metabolite, which is much more active than fesoterodine *in vitro* and *in vivo* (x100 times more affinity for muscarinic receptors *in vitro* than fesoterodine). SPM 7605 is therefore the main active pharmacological principle of fesoterodine. SPM 7605 is also the main metabolite of the marketed medicine tolterodine.

The cardiovascular system has been extensively investigated both *in vitro* and *in vivo*. Fesoterodine and SPM 7605 induced a concentration-dependent inhibition of hERG current with IC_{50} values of 3.6 and 0.5 µM, respectively. Blockade of the hERG-mediated potassium current has also been observed for some other antimuscarinic agents.

A dose-dependent tachycardia with no change in mean arterial pressure was observed in rats as expected from a muscarinic antagonist. *In vivo*, at a dose of 800 µg/kg i.v., decreases in diastolic blood pressure, heart rate and coronary artery blood flow and prolongation of the QT interval and QTc interval were noted in dogs.

Pharmacokinetics: fesoterodine is rapidly hydrolysed by non-specific plasma esterases to SPM 7605 in all animal species investigated including man except for the dog in which the rate of hydrolysis is slower. The *in vitro* metabolism of fesoterodine is most different in the rat, which is considered a less relevant species.

In repeat-dose toxicity, the main target organ of toxicity was the liver in rats . No target organ of toxicity was identified in the mouse or the dog. Overall, in toxicity studies, animals were exposed at the NOAEL to total amounts of fesoterodine and its metabolites that little exceeded or almost were equal than that encountered at the highest clinical dose of fesoterodine.
Fesoterodine was not genotoxic or carcinogenic.

Reproduction studies have shown minor embryo-toxicity (increased number of resorption, pre-implantation and post-implementation losses). This is mentioned in the SPC.

Phase II environmental studies will be completed after the marketing authorisation, as follow-up measures.

4. Clinical aspects

Introduction

The clinical development program for fesoterodine sustained-release (SR) included:

- Two double-blind Phase 3 trials (SP583, SP584) plus 2 long-term, open-label extension trials (SP738 and SP739),
- Two double-blind Phase 2 dose-defining trials (SP582 and SP668) plus a long term extension trial, SP669, which is still ongoing, and
- Seventeen Phase 1 trials to investigate the clinical pharmacology of fesoterodine SR (in one out of these seventeen studies an intravenous formulation was also tested).
- An immediate-release (IR) formulation of fesoterodine was used in two Phase 1 trials and a Phase 2a pilot trial (SP577).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The pharmacokinetics of fesoterodine have been characterised in healthy men and women over a single and multiple-dose range of 4 mg to 28 mg/day.

Nineteen Phase 1 trials, which included 753 subjects, have been completed to investigate the clinical pharmacology of fesoterodine. An immediate-release (IR) formulation of fesoterodine was used in 2 initial Phase 1 trials (Studies SP560 and SP561), including 75 subjects. In order to enhance patient compliance, a sustained release (SR) tablet was developed for a once daily administration. A total of 489 subjects received the SR formulation intended for approval; and 28 subjects received an intravenous formulation in addition to an SR formulation.

Fesoterodine metabolites were analysed using LC-MS/MS in plasma, urine and faeces. Fesoterodine was analysed in plasma using LC-MS/MS. The analytical method validations were found appropriate.

- Absorption

In vitro, the transport of fesoterodine, tolterodine and SPM 7605 across Caco-2 cell monolayers was investigated. The permeability coefficient of fesoterodine could not be determined due hydrolysis of fesoterodine to SPM 7605 in this study. The permeability constant for tolterodine and SPM 7605 were determined to be 1.0 10^{-5} cm/s and 2.5 x 10^{-6} cm/s respectively. For propranolol, which was used as one of the reference compounds and considered a highly permeable compound according to BCS, the permeability coefficient was determined to be 1.1 x 10^{-5} cm/s.

In vitro studies have been also conducted with both fesoterodine and its major metabolite SPM 7605 to characterize whether they are substrates and / or inhibitors of P-gp. These *in vitro* studies indicate that both fesoterodine and SPM 7605 are substrates for P-gp (ATPase Km values = 56 and 105 µM) and that both compounds are weak inhibitors of the P-gp mediated transport of digoxin in Caco-2 cells (IC50 values of 131 and >300 µM) respectively. Consequently, the likelihood of clinically relevant P-gp inhibition on fesoterodine and SPM 7605 is considered to be low in clinical practice given the wide margin between IC_{50} and maximal systemic concentrations.

After administration of the IR formulation, t_{max} is reached after approximately 0.5-1 hour. The rate of absorption across all Phase 1 trials is comparable with t_{max} being approximately 5 hours for the prolonged release formulation.

The rate of absorption is constant over the dose range of 4 to 28 mg fesoterodine and is comparable after single or multiple-dose administration. The C_{max} levels after a single dose of 4 and 8 mg of the prolonged release tablets were in mean values approximately 1.90-2.20 ng/ml and 3-6 ng/ml respectively (data from all phase I studies, no food interaction). See table 1 for a comparison between the immediate release and the prolonged release formulation.

Table 1. Pharmacokinetic parameters after single and multiple doses administration of IR (4 mg presented) and prolonged release formulations (4 and 8 mg presented). (Mean±SD). At both day 3 and day 7 steady state has been reached (multiple doses).

PK-parameter	Repeated dosing 3 days (day 3) qd prolonged	Repeated dosing 3 days (day 3) qd prolonged	Repeated dosing IR formulation bid	Single dose prolonged release formulation	Single dose IR formulation 4 mg	Single dose IR formulation 4 mg

	release 4 mg (SP 566) n=6	release 8 mg (SP 566) n=6	4 mg (day 7) (SP 561) n=9	(day 1) 4 mg (SP 566) n=6	(Day 1) (SP 561) n=9	(SP 560) n=6
C_{max} (ng/ml)	2.12±1.28	5.15±2.02	6.98±3.66	2.19±0.66	6.88±3.31	6.38±1.60
C_{trough} (ng/ml)	0.37 ±0.19	0.74±0.33	-	-0.01 (0.02)	-	-
T_{max} (hr), median (range)	4.17 ± 2.04*	5.00±0.00*	0.50-1.00 (0.50-2.00)	5.17±0.75	0.50-1.00 (0.50-1.50)	0.75-1.00 (0.5-3.00)
AUC_{0-24} ng.h/ml)	20.26 ±11.44	52.03 ±21.76	33.42± 19.66**	20.09±8.60***	28.45±14.95***	24.14±5.08***

*Mean±SD **AUC_{0-12} ***$AUC_{0-\infty}$

Maximum plasma levels of SPM 7605 are achieved approximately 5 hours after administration of fesoterodine SR. The rate of absorption is constant over the dose range of 4 to 28mg fesoterodine and is comparable after single or multiple-dose administration.

The absolute bioavailability of fesoterodine could not be determined, due to the rapid hydrolysis of fesoterodine to SPM 7605. Fesoterodine was only measurable after i.v. administration. The bioavailability of SPM 7605 after oral administration of 8 mg fesoterodine could be determined to be 52 % compared to fesoterodine i.v. and 42 % compared to SPM 7605 i.v.

Exposure to SPM 7605 was 22% increased in the fed state as compared to the fasted state. Although bioequivalence between the 2 treatments could not be demonstrated the difference is considered not to be clinically relevant. Therefore, dose adjustment with regard to food is not necessary.

- Distribution

The apparent volume of distribution of SPM 7605 was 169L (CV 17.1%) following intravenous administration of SPM 7605 (study SP567),.

Plasma protein binding of SPM 7605 is approximately 50%, with a similar affinity to human serum albumin and alpha1-acid glycoprotein.

- Metabolism and Excretion

Fesoterodine functionally acts as a pro-drug. After oral administration, fesoterodine is rapidly and extensively hydrolyzed to its active metabolite SPM 7605.

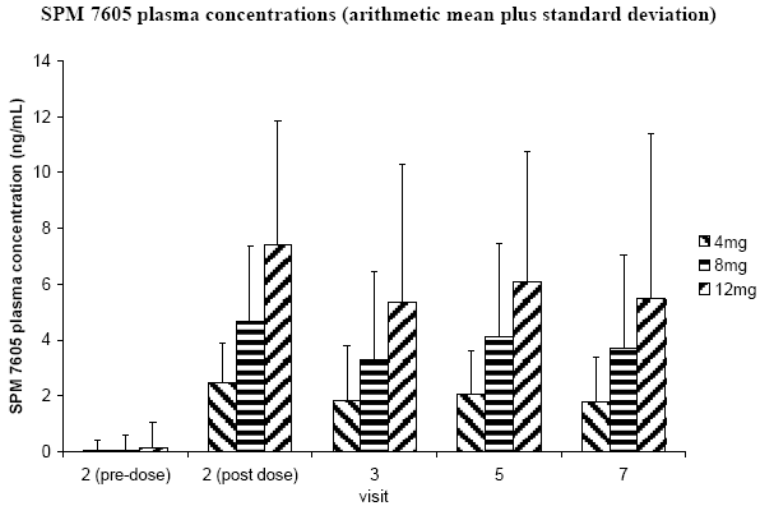
Hepatic metabolism and renal excretion contribute significantly to the elimination of SPM 7605 Clearance of SPM 7605 was approximately 42 L/h after i.v. administration. The mean terminal half-life was approximately 4-4.5 hours after i.v. administration and 6-9 hours after administration of the prolonged release formulation. This suggests an absorption-rate limited elimination for the prolonged release formulation. SPM 7605 is metabolized to its carboxy (SPM 5509), carboxy-N-desisopropyl (SPM 7790) and N-desisopropyl metabolite (SPM 7789).

The data suggests that CYP3A4 and CYP2D6 are involved in the metabolism, but are probably not the only enzymes involved, possibly CYP2A6 can be involved in the formation of SPM 7789. SPM 5509 is also formed in poor metabolisers, indicating that there must be another enzyme other than CYP2D6 that is able to catalyse this metabolic pathway. In vivo metabolite profiling was performed up to 96 hours. When the excretion pattern of fesoterodine, SPM 7605 and subsequent metabolites was evaluated, approximately 77 % of the dose after oral administration and 85 and 86 % after fesoterodine i.v. and SPM 7605 i.v. was recovered in urine and faeces. No biliary elimination seems to occur because almost no SPM 7605 is found in faeces after i.v. administration. There was a more extensive formation of SPM 5509, SPM 7789 and SPM 7790 after oral administration, indicating first-pass metabolism. It seems that an almost complete absorption occurs (based on similar urinary excretion of metabolites SPM 5509, 7789 and 7790 after oral and i.v. administration), however it

cannot be excluded that some metabolites are formed presystemically and then subsequently absorbed. The fraction of SPM 7605 excreted unchanged in urine after oral, fesoterodine i.v. and SPM 7605 i.v. was approximately 16 %, 27 % and 34% respectively. The presence of SPM 7605 in the faeces after oral administration but not after i.v. administration indicates intestinal hydrolysis.

- Target population

Pharmacokinetic parameters in the target population were measured in two Phase 2 (SP582 and SP668) and one Phase 3 (SP584) clinical trials.



- Special populations

Exposure to SPM 7605 is approximately doubled in poor CYP2D6 metabolisers as compared to extensive metabolisers, while the terminal half-life of SPM 7605 is not changed in poor metabolisers. Exposure to the carboxy metabolite and to the carboxy-N-desisopropyl metabolite is decreased by approximately 50% as compared to extensive CYP2D6 metabolisers.

Gender, age or race do not influence the PK behaviour of fesoterodine. In subjects with moderate hepatic impairment the exposure to SPM 7605 was increased 2-fold after a single dose of fesoterodine. CYP2D6 function was the most affected with a subsequent decrease of the related metabolites. The dose of fesoterodine has been limited to 4 mg in patients with moderate hepatic impairment. In subjects with severe hepatic impairment, fesoterodine is contraindicated.

In subjects with mild, moderate or severe renal impairment unbound exposure was 1.3, 1.5 and 1.8 fold higher compared to healthy extensive metabolisers. A larger effect is expected in patients with CYP2D6 poor metaboliser status. In patients with mild and moderate renal impairment the dose should therefore be increased from 4 to 8 mg with caution. In patients with severe renal impairment, the dose is restricted to 4 mg.

Considering the risk of higher exposure associated with dose-dependent side effects in certain subpopulations such as CYP2D6 poor metabolisers and the absence of genotyping a starting on a dose of 4 mg is recommended. The dose can then be titrated based on dose-dependent side-effects and needs of the patient. These dosing recommendations are reflected in the SPC (sections 4.2, 4.4 and 4.5). The concomitant use of potent CYP3A4 inhibitors in subjects with moderate to severe hepatic or renal impairment is contra-indicated and mentioned in the SPC.

- Pharmacokinetic interaction studies

Based on *in vitro* data, it is likely that fesoterodine can inhibit CYP3A4 in the intestine, although the risk of a clinical significant interaction with midazolam and other substances with substantial intestinal CYP3A4 metabolism seems low. Some inhibition of CYP2B6 was found, however this is not expected to give rise to a clinically relevant interaction given the large margin between inhibitory

concentrations found in vitro and plasma levels obtained. No relevant inhibition of CYP2C8 or CYP2E1 was found. The weak inhibition P-gp by SPM 7605 and fesoterodine is not likely to have any clinical relevance.

Concomitant treatment with a CYP3A4 inhibitor resulted in a 2-fold increase of exposure to SPM 7605. Both extensive and poor CYP2D6 metabolisers experienced similar increase. Potentially, up to a 4-fold increase of exposure compared the standard recommended treatment might be expected.

No interactions have been observed between fesoterodine and oral contraceptives.

- Dose proportionality and time dependencies

Fesoterodine displays dose-proportional pharmacokinetics in the dose-range from 4 to 12mg/day (SP565).

There are no indications of time dependent pharmacokinetics . No accumulation of SPM 7605 was observed.

Pharmacodynamics

- Mechanism of action

Binding of fesoterodine and several of its *in vivo* metabolites to human recombinant muscarinic acetylcholine receptors (M1-M5) was investigated in competition binding experiments. There was no selectivity of SPM 7605 in binding to these receptors. Fesoterodine was at least 100-fold less potent. The carboxy metabolite (SPM 5509) and the N-desisopropyl metabolite (SPM 7833) showed uniform binding affinity to all muscarinic receptor subtypes as well, albeit with more than 50-fold and about 20- to 70-fold lower affinity respectively as compared to SPM 7605. The carboxy-N-desisopropyl metabolite (SPM 6923) did not bind to any of the muscarinic receptors up to a concentration of 1 µmol/L.

Neither the S-enantiomers of fesoterodine and SPM 7605 nor the corresponding racemates have a more than intermediate level of binding at any of the human muscarinic receptors. Fesoterodine or SPM 7605 do not show specificity to other receptors (such as dopamine, serotonin, adrenaline, neuropeptide, sigma) or ion-channels tested (eg, sodium, calcium, chloride). The lack of selectivity was also seen in ex vivo tissue studies.

- Primary and Secondary pharmacology

Primary pharmacodynamics
Two urodynamic studies were conducted: SP577 and SP668.
SP577 was a preliminary Phase 2 study in which 12 subjects with urodynamic confirmed detrusor instability were treated with the immediate release fesoterodine formulation (2 and 4 mg) for 4 weeks. The volume at first unstable contraction was measured as the primary variable. After treatment an increase of 43.8 ml and 81.5 ml respectively in urinary volume were measured. Some other urodynamic parameters showed a trend of improvement compared to placebo. However, the small number of subjects available, the IR formulation used, the high variability observed, and the doses studied (placed in the lower limit of the dosage range finally recommended) provide little helpful information.

SP668 study, also discussed below (dose response studies) is a double-blind, placebo-controlled, fixed dose trial, where 3 doses of fesoterodine (4, 8 and 12 mg) were tested. The study enrolled male and female patients (18 to 78 years of age inclusive) with symptoms or signs of overactive bladder with increased urinary frequency and urinary incontinence. Subjects were stratified into 2 balanced strata by the presence or absence of involuntary detrusor contraction as measured during the filling phase of baseline cystometry. A second urodynamic assessment was made only in patients with involuntary detrusor contractions. Changes in volume at first involuntary contraction, in volume at first and at strong desire to void, in maximum cystometric capacity and in compliance were measured.

After 8 weeks of treatment an increase of bladder volumes was observed for fesoterodine groups with respect to placebo. Dose-dependent improvement was also noted for most of the volumes measured. The small size of the groups and the lack of a measurement in the group without urodynamic findings in cystometry limit the value of these results.

Secondary pharmacodynamics
Fesoterodine induced a decrease in saliva volume, mainly when doses equal or higher than 12 mg were administered. This was supported by the patients' view. A greater decrease was reported in elderly compared to young males after a single dose of 8 mg.

Fesoterodine showed a clear trend to increase the residual urinary volume in a dose-dependent manner. Maximum tolerated dose was considered 28 mg with a maximum of > 400 ml in one healthy volunteer. After a single dose of 8 mg elderly volunteers experienced a greater increase than young subjects did.

Heart rates increased with a clear dose-dependent relationship. Pupillary reaction was also affected; this effect was more remarkable for increasing doses. A QT study was conducted in healthy volunteers. The safety implications of these findings are discussed under Safety.

In summary, fesoterodine (in fact SPM 7605) exerted the expected urodynamic action. According its PD profile, negative effects in urinary retention, dryness of mouth and blurred vision were revealed. These findings were more evident for the highest doses and the elderly population.

Coadministration of fesoterodine with other antimuscarinic agents may increase the anticholinergic pharmacological actions and result in, increasing frequency or severity of dry mouth, constipation, urinary retention and other anticholinergic pharmacological side effects, and coadministration should therefore be avoided. This is reflected in the SPC (section 4.5).

Clinical efficacy

- Dose response studies

The Phase 2 program started with study SP577, a Phase IIa pilot trial that investigated the effects of fesoterodine Immediate release (IR) formulation 2mg and 4mg twice daily on urodynamic parameters in 12 female subjects with OAB. The urodynamic effect on the volume at first involuntary contraction and bladder capacity were assessed.

Study subjects had a mean ages of 60 years and had symptoms of bladder overactivity and confirmed detrusor instability (>10 cmH_2O) at urodynamic visit 1.

Study result showed that administration of fesoterodine immediate release 2 or 4mg increased the volume at first involuntary contraction and bladder capacity in a dose dependent manner.
The improvement was comparable to results shown with other antimuscarinic compounds.

The Phase 2a pilot trial was followed by two double-blind, dose-defining trials using a slow release formulation (SR), study SP582 and study SP668.

The following table presents an overview of the Phase 2 trials conducted using an SR formulation of fesoterodine in subjects with OAB.

Trial number/clinical development phase/trial design/dosage	Subjects receiving fesoterodine	Subjects receiving placebo	Treatment duration for fesoterodine
SP582/Phase 2/ multicenter, randomized, double-blind, placebo-controlled, parallel-group dose-ranging trial to investigate efficacy and safety in OAB/ fesoterodine 4, 8, and 12mg doses once daily	4mg/day: 186 8mg/day: 173 12mg/day: 186	183	12 weeks
SP668/Phase 2/ multicenter, stratified, randomized, double-blind, placebo-controlled, parallel-group, urodynamic trial to investigate efficacy, safety, and dose-response in OAB/ fesoterodine 4, 8, and 12mg doses once daily	4mg/day: 43 8mg/day: 47 12mg/day: 38	43	8 weeks
Total	**673**	**226**	**—**

Methods

These studies enrolled male or female subjects (18 to 78 years of age inclusive) with symptoms or signs of overactive bladder with increased urinary frequency and urinary incontinence. Most of the subjects randomised to double-blind treatment in these Phase 2 trials were female: 85% in SP582 (FAS) and 87% in SP668 (FAS). The trial populations were primarily Caucasian (81% to 99%). Ages ranged from a minimum of 18 years to a maximum of 79 years and were similar between trials; median ages overall ranged from 55 to 57 years. Demographic and Baseline characteristics were generally similar among treatment groups within each of these trials. Patients included in SP668 seemed more affected. Higher percentage of subjects reported both prior and concomitant diseases although only 16% of patients enrolled in SP668 vs 64% of subjects in SP582 had at least 1 prior medication.

In both trials, there was a considerable time since first diagnosis of OAB (4 years in SP582 and 6 years in SP668). About one third of patients included in both trials (31% in SP582 and 28% in SP668) had received prior treatment for the condition, mainly with oxybutynin and tolterodine.

The selection criteria for SP582 and SP668 were common in most aspects, but in SP668 patients underwent a new urodynamic examination at Baseline. It results in a rather heterogeneous Phase 2 population composed of patients with "at least 1 involuntary detrusor contraction in a urodynamic examination in the prior year (SP582 subjects), patients with documented detrusor contractions at baseline in a standardised cystometry (SP668 Stratum A subjects) and patients with documented normal urodynamic findings (SP668 Stratum B subjects).

No pre-specified degree of severity was required. Subjects included had baseline mean of 11 to 12 micturitions per 24 hours. The baseline mean number of incontinence episodes was more variable, ranging from 17 to 24 episodes per week. Regarding incontinence, the population included can be considered in general as of moderate severity.

Results

Micturitions per 24 hours – Mean change from baseline (End of Treatment) in dose finding studies (SP582 and SP668)

SP582				
Dose Group	**Micturitions / 24 h Baseline (SD)**	**Mean change from baseline EOT (SD)**	**ANCOVA adjusted estimate for difference from placebo (95%CI)**	**p-value**

Placebo (N=178)	10.92 (2.989)	-1.42 (2.88)		
FST 4mg (N=182)	11.06 (2.891)	-2.20 (2.98)	-0.72 (-1.23, -0.21)	0.0030*
FST 8mg (N=164)	11.15 (2.634)	-2.37 (2.30)	-0.82 (-1.35, -0.29)	0.0012*
FST 12mg (N=174)	11.07 (3.190)	-2.41 (2.69)	-0.94 (-1.46, -0.42)	0.0002*
SP668				
Placebo (N=42)	10.93 (2.119)	–0.50 (2.852)		
FST 4mg (N=43)	11.11 (3.270)	–1.55 (2.346)	–0.996 (–1.97, –0.02)	0.0446*
FST 8mg (N=45)	11.37 (2.933)	–2.43 (2.058)	–1.815 (–2.78, –0.85)	0.0003*
FST 12mg (N=36)	11.88 (2.598)	–2.55 (2.191)	–1.784 (–2.81, –0.76)	0.0007*
Stratum A				
Placebo (N=23)	11.59 (2.209)	–0.04 (3.361)		
FST 4mg (N=25)	11.43 (3.325)	–1.54 (2.214)		
FST 8mg (N=27)	11.59 (3.168)	–2.86 (1.909)		
FST 12mg (N=20)	12.06 (2.255)	–2.58 (2.436)		
Stratum B				
Placebo (N=19)	10.14 (1.746)	–1.07 (2.029)		
FST 4mg (N=18)	10.67 (3.234)	–1.55 (2.585)		
FST 8mg (N=18)	11.05 (2.595)	–1.79 (2.157)		
FST 12mg (N=16)	11.64 (3.035)	–2.52 (1.920)		

In SP 582 improvements were also shown for the second most important primary efficacy endpoint (change in average number of urge incontinence episodes per week) with statistical significance achieved in the fesoterodine 12mg group.

A dose related increase of most of bladder volumes was observed after 8 week treatment. Fesoterodine appears to exert a more defining effect in the urodynamic setting than in symptomatic one.

In conclusion, phase 2 studies are consistent in finding a statistically significant greater response for fesoterodine groups than for placebo in terms of reduction of frequency of micturitions and incontinence episodes. The dose-response relationship is apparent in the range 4-8 mg, getting almost flat beyond that. This holds especially true regarding incontinence episodes. Due to the limited sample size of study SP668, no firm conclusions can be drawn on a differential clinical effect of fesoterodine depending on the baseline urodynamic findings.

- Main studies

The efficacy and safety of fesoterodine in the treatment of OAB has been studied in 2 randomised, placebo-controlled, fixed dose Phase 3 trials (Studies SP583 and SP584).
The doses studied in the Phase 3 program included fesoterodine 4 mg and 8 mg once daily (od). The active comparator used was tolterodine 4mg od.

The following table presents an overview of the Phase 3 trials conducted using an SR formulation of fesoterodine in subjects with OAB.

Trial number/clinical development phase/trial design/dosage	Subjects receiving fesoterodine	Subjects receiving placebo	Subjects receiving active control	Treatment duration for fesoterodine
SP583/Phase 3/ multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled (tolterodine), parallel-group trial.	4mg/day: 272 8mg/day: 287	283	Tolterodine SR 4mg/day: 290	12 weeks
SP584/Phase 3/ multicenter, randomized, double-blind, placebo-controlled, parallel-group trial.	4mg/day: 282 8mg/day: 279	271	NA	12 weeks
Total	**1120**	**554**	**290**	**—**

METHODS

SP583 and SP584 were randomized, double-blind, placebo-controlled, parallel-group and 12 weeks treatment duration studies. SP583 was carried out in Europe, South Africa, Australia, and New Zealand and SP584 was carried out in the US.

The duration of the trial per subject was approximately 16 weeks: a 2-week placebo run-in period, a 12-week double-blind treatment period, and a 2-week safety follow-up period.

Study Participants

Subjects were to be males and females ≥18 years of age with

- symptoms or signs of OAB syndrome (known from medical history) and are expected to exhibit them at the specified level during the run-in period:
  - urinary urgency: at least 6 (later amended to 3) urinary urgency episodes documented during the 3-day diary period.
  - increased micturition frequency (with/without incontinence, for at least 6 months before enrollment): at least 8 micturitions per 24 hours confirmed on each day of the 3-day diary period.
  - urinary urge incontinence (for at least 1 month before enrolment): at least 3 urinary urge incontinence episodes documented during the 3-day diary period.
- subject has documented the voided volume for 1 complete day during the 3-day diary period
- subject has documented (based on Likert scale), that his/her condition causes him/her at least moderate problems.

Patients with prior treatments with drug or non-drug treatment for OAB, amantadine, class Ia and III antiarrhythmic drugs and those who had any known neurological disease influencing bladder function, lower urinary tract pathology, a residual urine volume > 100 mL or clinically relevant bladder outlet obstruction or had predominantly symptoms of stress incontinence were not eligible for pivotal studies.

A relevant Protocol Amendment (dated 26 Apr 2004) included revisions to 2 inclusion criteria to add subjects with urinary urge incontinence at Baseline known from medical history and to include subjects with at least 3 urinary urge incontinence episodes documented during the 3-day diary period. The option to have "at least 6 urinary urgency episodes" instead of the documented urge incontinence episodes was eliminated.

Treatments

Patients were randomised to placebo, fesoterodine 4mg/day, and fesoterodine 8mg/day. In addition to a placebo control, SP583 also included an active control, tolterodine SR (4 mg once daily).

Objectives

The objective of the trial was to investigate the efficacy, tolerability, and safety of fesoterodine

as compared to placebo and active control in subjects with OAB.

SP584 also included genotyping for assessment of the CYP2D6 metabolisation status (poor vs extensive metabolizer) and a population pharmacokinetics analysis of SPM 7605, the active metabolite of fesoterodine.

Outcomes/endpoints

Both Phase 3 studies assessed the same **primary efficacy variable**: "Change in the average number of micturitions (frequency) per 24 hours after 12 weeks of treatment". There were differences between the co-primary efficacy variables between the Europe and US

Co-primary variable for submission in Europe: 'Treatment response derived from a treatment benefit scale after 12 weeks of treatment'. Subjects were asked to compare their present condition with their situation before the start of the trial: My condition has been: 1=greatly improved, 2=improved, 3=not changed, 4=worsened, during treatment. The treatment response was set to 'YES' if the category on the Treatment Benefit Scale was '1' or '2' and to 'NO' if the category on the scale was '3' or '4'.
Co-primary variable for submission in the US: Change in average number of urge incontinence episodes per 24 hours (from baseline to value after 12 weeks of treatment).

Therefore **three** primary/co-primary endpoints were used in both pivotal trials.

Secondary endpoints in both phase 3 trials included (but were not limited to) number of continent days per week, voided volume per micturition.
Health outcome variables included the change in the subject's evaluation of quality of life using 2 validated questionnaires: the King's Health Questionnaire (KHQ) and the International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF).

Randomisation/Blinding (masking)

The randomization procedure anticipated a balancing of treatments (1:1:1:1 for placebo; fesoterodine 4mg/day, fesoterodine 8mg/day, tolterodine 4mg/day) across countries and sites.

Placebo tablets were identical in appearance (size and color) to fesoterodine 4mg and 8mg tablets. Placebo capsules (encapsulated) were identical in appearance to encapsulated tolterodine 4mg capsules (encapsulated) given orally once daily. In addition, all accompanying packaging was identical in appearance. Blinding was maintained by inclusion of matching placebos for the non-active dosage forms (double dummy design).

Statistical methods/Sample size

Six analysis sets were defined:

- Screened Set (SCS): The subjects who had signed an informed consent and completed a Visit 1 assessment.
- Enrolled Set (ES): The ES included those subjects from the SCS who entered the Run-In Period (obtained at least 1 dose of placebo).
- Randomized Set (RS): The RS included all subjects randomized in the trial.
- Safety Set (SS): The SS defined all subjects who took at least 1 dose of trial medication after randomization.
- Full Analysis Set (FAS): The FAS consists of all subjects in the SS, who had at least 1 valid post-Baseline efficacy measurement.
- Per Protocol Set (PPS): An analysis was carried out excluding subjects from the FAS who had major protocol deviations (determined during blind data review) and/or with duration of double-blind treatment shorter than 2 weeks.

The primary analysis set for efficacy in all statistical analyses was the Full Analysis Set (FAS). The measurements of the continuous primary and secondary variables prior to first administration of the trial medication were used as Baseline measurements. The measurements in the last completed valid diary of the Double-Blind Treatment Period were used as endpoint values.

Statistical analyses for the primary variables of micturition and urge incontinence were performed using standard ANCOVA techniques including treatment and country/region as factors and baseline value as a covariate. Treatment response was analyzed using asymptotic normal approximation methodology. A sequentially rejective closed-test procedure was applied.

The imputed endpoint values from the last observation carried forward (LOCF) method to account for the missing values for early dropouts were used in the primary analysis. A sensitivity analysis was conducted based on observed cases (eg, missing values were not imputed). The ANCOVA results at the end of treatment (LOCF) among subjects who dropped out of the trial early are also presented for an exploratory comparison with trial completers. Further, a sensitivity analysis was performed by removing extreme outliers from the FAS. During the blinded data review meeting for SP583, it was decided to remove extreme outliers from the FAS and to perform a sensitivity analysis. The same criteria for this sensitivity analysis were used for SP584 as a post-hoc analysis. Further, a non-parametric sensitivity analysis was performed using the Wilcoxon rank sum test.

The following is a brief summary of the statistical analysis for the primary variables for the 2 regions. Both hierarchical testing procedures for the primary variables are considered closed-testing procedures that preserve the multiple alpha level without adjustment of the nominal significance level.

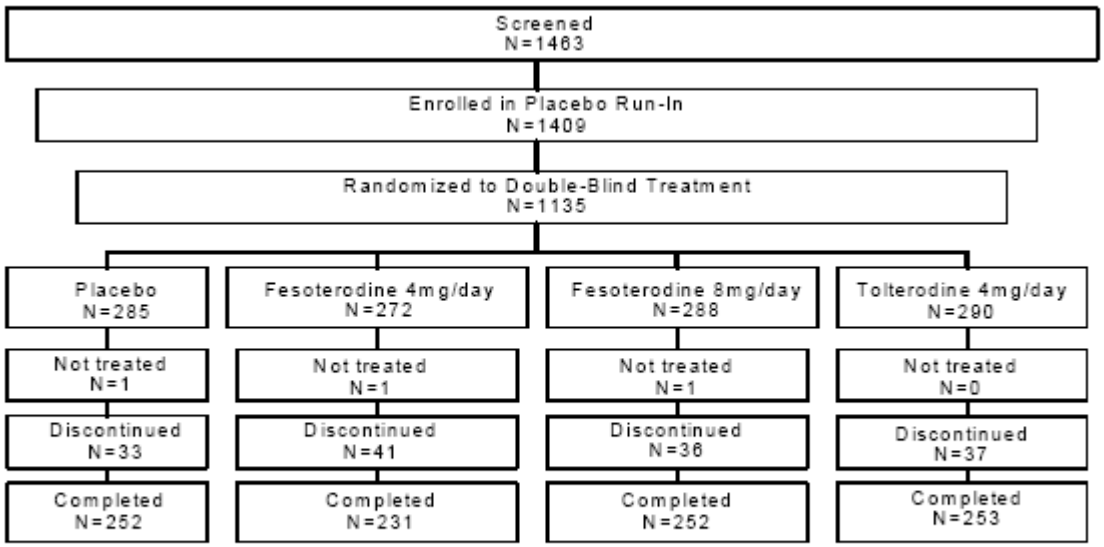
	Analysis method – US FDA	**Analysis method - EU Regulatory Authorities**
Variables	• Change in average number of micturitions per 24 hours • Change in average number of urge incontinence episodes per 24 hours	• Change in average number of micturitions per 24 hours • Treatment response (Yes/No variable) derived from a 4-category Treatment Benefit Scale
Primary analysis set	FAS	FAS
Analysis method	LOCF method was applied to account for missing values for dropouts. Data were analyzed in a main effect ANCOVA model with terms for treatment and site (properly pooled) and Baseline as a covariate.	Change in average number of micturitions per 24 hours: LOCF method was applied to account for missing values for dropouts. Data were analyzed in a main effect ANCOVA model with terms for treatment and site (properly pooled) and Baseline as a covariate. Treatment response: LOCF method was applied to account for missing values for dropouts. Binary data were analyzed and response rates were compared by using the normal approximation method.
Testing procedures	Step 1: Fesoterodine 8mg/day vs placebo for micturitions, if statistically significant then go to step 2; otherwise stop. Step 2: Fesoterodine 4mg/day vs placebo for micturitions, if statistically significant then go to step 3; otherwise stop. Step 3: Fesoterodine 8mg/day vs placebo for urge incontinence episodes, if statistically significant then go to step 4; otherwise stop. Step 4: Fesoterodine 4mg/day vs placebo for urge incontinence episodes, determine if statistically significant.	Step 1: Fesoterodine 8mg/day vs placebo for micturitions and treatment response, if both statistically significant then go to step 2; otherwise stop. Step 2: Fesoterodine 4mg/day vs placebo for micturitions and treatment response, determine if statistically significant.

RESULTS

Participant flow

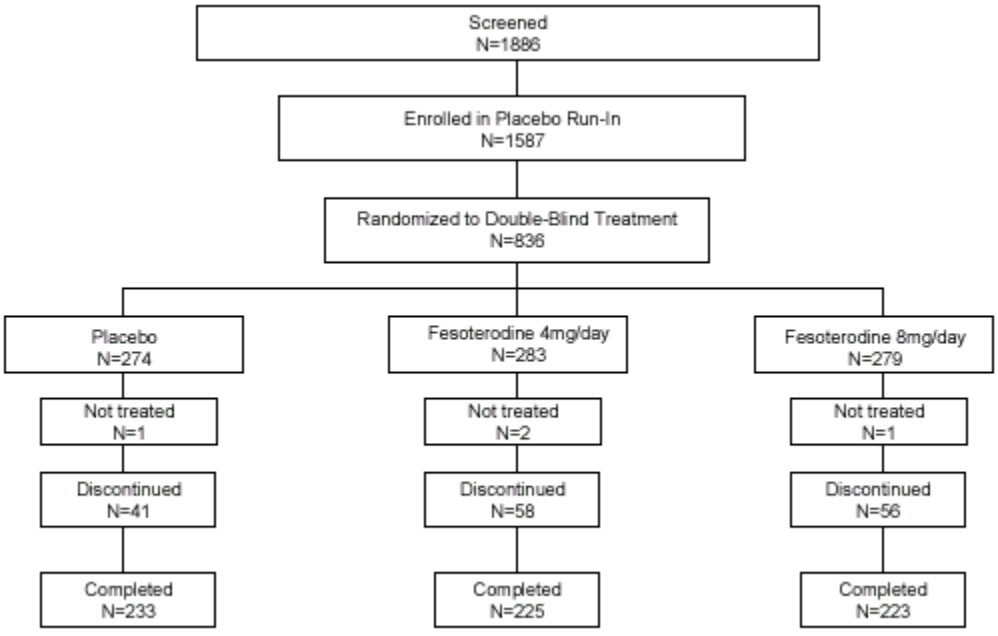
An overview of subject disposition is provided by the following flow charts:

Study SP 583



Data source: Table 2.1 and Table 3.1

Study SP 584



Data source: Table 2.1, Table 3.1.1

Recruitment

SP 583: 264 (19%) of enrolled subjects were prematurely withdrawn from the trial as run-in failures. The most common reason for discontinuation from the Screening and Placebo Run-In Periods was ineligibility to continue trial (185/1463; 13%).

SP 584: 751 (40%) of screened subjects were prematurely withdrawn from the trial. The most common reason for discontinuation was ineligibility to continue in the trial (590/1886; 31%).

Most subjects (≥80% in any treatment group) completed the full 12 weeks of treatment in both studies

Conduct of the studies

During the double blind treatment period, 96% to 100% of subjects in each treatment group were compliant with respect to trial medication.
A slight increased discontinuation due to adverse events with higher doses of fesoterodine was observed.

Baseline data

About 80% of the subjects were female and 20% were male subjects. The trial population was primarily white. Ages ranged from 19 years to 91 years (mean 58 years). A total of 33% of patients were ≥65 years of age and 11% were ≥75 years of age.

The population was largely made up of subjects with long-term, established diagnosis of OAB.
Baseline micturition frequency and incontinence episodes somewhat representing severity of OAB, were comparable between the different treatment groups.

Subjects in each treatment group had Baseline means of about 12 to 13 micturitions per 24 hours and 4 urge incontinence episodes per 24 hours. Notable is the wide range of micturition frequency. However the numbers are comparable between groups.

At least three quarters (75% to 85%) of the subjects in each treatment group were incontinent at baseline.
Demographic characteristics regarding age, gender, concomitant diseases and therapies and prior treatment for OAB were comparable across the 4 treatment groups and the trial population is representative for patients with OAB.

Numbers analysed

SP 583: the Full Analysis Set (FAS) included a total of 1103 subjects. A total of 6% to 8% of subjects had LOCF imputations for the change in number of micturitions per 24 hours, 4% to 7% had LOCF imputations for the change in number of urge incontinence episodes per 24 hours, and 9% to 13% had LOCF imputations for response on the treatment benefit scale. A total of 87% to 91% of subjects in each treatment group completed double-blind treatment.

SP 584: the FAS included a total of 800 subjects; a total of 11% to 16% of subjects had LOCF imputations for the change in number of micturitions per 24 hours, 11% to 15% had LOCF imputations for the change in number of urge incontinence episodes per 24 hours, and 15% to 18% had LOCF imputations for response on the treatment benefit scale.

Outcomes and estimation

Primary efficacy endpoints

Both pivotal studies (SP 583 and SP 584) where fesoterodine was tested at fixed dose demonstrated a statistically significant reduction in the 3 principal variables (number of micturitions in 24 hours, number of urge incontinence episodes in 24 hours, and treatment response).

- Change in average number of micturitions per 24 hours

-

Pivotal trials.- Descriptive summary of number of micturitions / 24 hours (FAS and PPS)				
Treatment for OAB	**Full Analysis Set (FAS) Mean (SD)**		**Per Protocol Set (PPS) Mean (SD)**	
	Observed value	**Change from baseline**	**Observed value**	**Change from baseline**
SP583				
PCB **Baseline** **EOT (LOCF)**	N = 279 12.0 (3.69) 10.9 (4.23)	 -1.02 (2.974)	N = 262 12.1 (3.65) 11.0 (4.26)	 - 1.09 (2.794)
FST 4 mg **Baseline** **EOT (LOCF)**	N = 265 11.6 (3.22) 9.8 (3.18)	 -1.74 (2.660)	N = 245 11.8 (3.19) 9.9 (3.27)	 -1.86 (2.649)
FST 8 mg **Baseline** **EOT (LOCF)**	N = 276 11.9 (3.81) 10.0 (4.37)	 -1.94 (3.146)	N = 253 12.1 (3.75) 9.9 (4.43)	 -1.94 (3.024)
TLT 4 mg **Baseline** **EOT (LOCF)**	N = 283 11.5 (2.92) 9.8 (3.01)	 -1.69 (2.415)	N = 266 11.6 (2.79) 9.9 (2.98)	 -1.74 (2.373)
SP584				
PCB **Baseline** **EOT (LOCF)**	N = 266 12.2 (3.66) 11.2 (3.44)	 -1.02 (3.387)	N = 241 12.3 (3.40) 11.3 (3.41)	 - 1.02 (2.940)
FST 4 mg **Baseline** **EOT (LOCF)**	N = 267 12.9 (3.86) 11.0 (3.56)	 -1.86 (3.645)	N = 230 12.9 (3.48) 11.0 (3.42)	 -1.94 (3.088)
FST 8 mg **Baseline** **EOT (LOCF)**	N = 267 12.0 (3.31) 10.1 (3.19)	 -1.94 (2.974)	N = 238 12.1 (3.10) 10.1 (3.16)	 -1.96 (2.638)

The change in micturition frequency results for PPS was consistent with those observed in the FAS with LOCF for the primary analysis.

- Change in average number of urge incontinence episodes per 24 hours

Pivotal trials.- Descriptive summary of urge incontinence / 24 hours (FAS and PPS)				
Treatment for OAB	**Full Analysis Set (FAS) Mean (SD)**		**Per Protocol Set (PPS) Mean (SD)**	
	Observed value	**Change from baseline**	**Observed value**	**Change from baseline**
SP583				
PCB **Baseline** **EOT (LOCF)**	N = 211 3.7 (3.13) 2.5 (3.54)	 -1.20 (3.256)	N = 202 3.6 (3.00) 2.4 (3.41)	 -1.20 (3.264)
FST 4 mg **Baseline** **EOT (LOCF)**	N = 199 3.8 (3.38) 1.8 (2.96)	 -2.06 (2.704)	N = 188 3.9 (3.42) 1.8 (3.01)	 -2.07 (2.766)
FST 8 mg **Baseline** **EOT (LOCF)**	N = 223 3.7 (2.97) 1.4 (2.46)	 -2.27 (2.396)	N = 207 3.7 (2.95) 1.4 (2.37)	 -2.32 (2.443)

TLT 4 mg **Baseline** **EOT (LOCF)**	N = 223 3.8 (3.07) 2.0 (3.04)	 -1.83 (2.320)	N = 210 3.8 (3.12) 2.0 (3.01)	 -1.84 (2.307)
SP584				
PCB **Baseline** **EOT (LOCF)**	**N** = 205 3.7 (3.33) 2.7 (3.31)	 -1.00 (2.749)	N = 182 3.6 (3.19) 2.6 (3.20)	 -0.93 (2.710)
FST 4 mg **Baseline** **EOT (LOCF)**	N = 228 3.9 (3.51) 2.1 (3.24)	 -1.77 (3.163)	N = 198 3.7 (3.31) 2.1 (3.20)	 -1.70 (3.116)
FST 8 mg **Baseline** **EOT (LOCF)**	N = 218 3.9 (3.32) 1.4 (2.13)	 -2.42 (2.764)	N = 193 3.8 (3.18) 1.4 (2.19)	 -2.34 (2.665)

The change in the average number of urge incontinence episodes for the PPS was consistent with those observed in the FAS with LOCF for the primary analysis.

- Change in treatment response

Pivotal trials.- Summary of Treatment response (FAS)				
SP583				
Treatment for OAB	PCB n / N (%) N = 279	FST 4 mg n / N (%) N = 211	FST 8 mg n / N (%) N = 211	TLT 4 mg n / N (%) N = 211
EOT (LOCF) **Yes** **No**	 149/279 (53.4) 130/279 (46.6)	 198/265 (74.7) 67/265 (25.3)	 218/276 (79.0) 58/276 (21.0)	 205/283 (72.4) 78/283 (27.6)
EOT: Missing=Non-Response **Yes** **No**	 145/279 (52.0) 134/279 (48.0)	 194/265 (73.2) 71/265 (26.8)	 214/276 (77.5) 62/276 (22.5)	 201/283 (71.0) 82/283 (29.0)
Early Termination **Yes** **No**	 4/ 8 (50.0) 4/ 8 (50.0)	 6/ 17 (35.3) 11/ 17 (64.7)	 3/ 10 (30.0) 7/ 10 (70.0)	 5/ 11 (45.5) 6/ 11 (54.5)
SP584				
Treatment for OAB	PCB n / N (%) N = 266	FST 4 mg n / N (%) N = 267	FST 8 mg n / N (%) N = 267	
EOT (LOCF) **Yes** **No**	 120/266 (45.1) 146/266 (54.9)	 170/267 (63.7) 97/267 (36.3)	 198/267 (74.2) 69/267 (25.8)	
EOT: Missing=Non-Response **Yes** **No**	 145/279 (52.0) 134/279 (48.0)	 194/265 (73.2) 71/265 (26.8)	 214/276 (77.5) 62/276 (22.5)	
Early Termination **Yes** **No**	 4/ 8 (50.0) 4/ 8 (50.0)	 6/ 17 (35.3) 11/ 17 (64.7)	 3/ 10 (30.0) 7/ 10 (70.0)	

Treatment response findings were consistent in the FAS (primary analysis) and PPS populations.

Both fesoterodine doses (4 and 8mg/day) showed statistically significant improvement over placebo at the end of treatment for the micturition and urge incontinence variables (US FDA analysis) and for the micturition and treatment response variables (EU analysis).

Secondary endpoints

Most symptoms related secondary variables also showed statistically significant difference from the baseline after 12 weeks treatment, with numerically better results for highest dose (8 mg/day).

Fesoterodine improved the signs and symptoms of OAB for all secondary endpoints in a comparable manner for both studies. A summary table for study SP 583 is given below:

SP 583.-Descriptive summaries of secondary endpoints (FAS)

Treatment for OAB	PCB Mean (SD) N = 279	**FST 4 mg** Mean (SD) N = 265	**FST 8 mg** Mean (SD) N = 276	**TLT 4 mg** Mean (SD) N = 283
Voided volume per micturitions				
Baseline	150.2 (52.04)	160.0 (59.53)	153.9 (56.88)	154.3 (52.90)
EOT	159.9 (62.02)	187.0 (92.55)	187.5 (73.72)	178.0 (66.24)
Change from baseline	9.77 (43.515)	26.97 (70.276)	33.46 (54.182)	23.60 (52.089)
Number of micturitions during daytime				
Baseline	10.1 (3.49)	9.6 (2.91)	9.9 (3.19)	9.5 (2.73)
EOT	9.4 (3.75)	8.3 (2.74)	8.3 (3.44)	8.2 (2.60)
Change from baseline	-0.72 (2.588)	-1.33 (2.450)	-1.51 (2.930)	-1.25 (2.197)
Nocturia				
Baseline	1.8 (1.23)	1.9 (1.34)	2.0 (1.56)	2.0 (1.23)
EOT	1.5 (1.35)	1.5 (1.33)	1.6 (1.73)	1.6 (1.28)
Change from baseline	-0.30 (1.120)	-0.41 (1.153)	-0.43 (1.154)	-0.44 (1.049)
Number of urgency episodes				
Baseline	11.1 (4.03)	11.0 (4.21)	11.5 (4.22)	11.0 (3.36)
EOT	10.3 (4.75)	9.1 (4.26)	9.0 (5.11)	9.0 (3.95)
Change from baseline	-1.14 (3.300)	-1.87 (3.075)	-2.43 (3.721)	-2.00 (3.187)
Number of total voidings				
Baseline	12.2 (3.72)	11.7 (3.28)	12.1 (3.73)	11.7 (2.96)
EOT	11.0 (4.23)	9.8 (3.21)	10.4 (4.43)	9.9 (3.06)
Change from baseline	-1.15 (2.937)	-1.87 (2.607)	-2.10 (3.111)	-1.81 (2.433)
Severity of urgency (Mild/Moder/Severe)				
Baseline (%)	13/50/32	9/51/34	12/51/31	12/48/33
EOT (%)	15/52/25	20/53/19	23/49/17	20/49/20
Number of continent days per week				
Baseline	0.8 (1.51)	0.8 (1.56)	0.6 (1.32)	0.6 (1.30)
EOT	2.9 (3.03)	3.6 (3.09)	4.0 (3.06)	3.1 (3.01)
Change from baseline	2.08 (2.871)	2.80 (3.046)	3.39 (3.050)	2.54 (2.978)

Health Outcomes Results

A small but consistent effect on quality of life as assessed by the King's Health Questionnaire in the fesoterodine was shown in pivotal trials.

Baseline scores in both pivotal studies were similar. Only one of the 9 domains, Impact of life scored over 50 points at baseline. No formal comparison was carried out. It has been suggested that a change of 5 or more points can be considered a clinical meaningful improvement, difference questioned by others. Assessing the changes from baseline with respect to placebo for the dosage finally chosen (4 mg) five out of 9 domains in Study SP583 and none in Study 584 reached the 5-minimal difference points. Regarding fesoterodine 8 mg dose 7 and 6 domains in each pivotal study scored at least 5 points more than placebo did.

- Analysis performed across trials (pooled analyses and meta-analysis)

Methods

Efficacy data from the double-blind pivotal trials SP583 and SP584 were pooled (Pool E1) to investigate selected subgroups. Efficacy in subsets of the population was evaluated in each of the primary trials (SP583 and SP584). Assignment of subjects to treatment groups followed the trial-specific rules, ie, pooled analysis of efficacy data was performed as randomized on the basis of the Full Analysis Set (FAS).

Results

Elderly patients (≥65 years) experienced a lower reduction of micturitions and patient reported response than younger subjects. On the contrary, a greater reduction in incontinence episodes was observed in that group, potentially related to a higher baseline rate in this subgroup.

Non-white subjects showed a lower reduction of incontinence episodes as well as some greater response in incontinence episodes. However the under-representation of non-Caucasian subjects and the higher variability do not allow conclusions to be drawn in this regard.

A higher placebo effect for the different endpoints is observed amongst naïve patients, which may be responsible of the observed differences in response. However, the differential effect from placebo is essentially similar.

- Clinical studies in special populations

No specific efficacy studies in special populations have been performed. However, characteristics such as age, gender, race and prior drug treatment have been analysed in the pivotal trials.

- Supportive studies

<u>Long-Term Exposure Trials: Sp669, Sp738, Sp739</u>

Subjects who completed the pivotal phase 3 studies SP583 or SP584 and the phase 2 study SP668 had the option to participate in long-term extension trials and receive fesoterodine up to 3 additional years to further evaluate its efficacy and safety. (ongoing studies)

Overview of the long-term trials conducted using an SR formulation of fesoterodine in subjects with OAB

Trial number/clinical development phase/trial design/dosage	Subjects receiving fesoterodine	Treatment duration for fesoterodine
SP669/Extension of SP668/ 2-phase multicenter, double-blind and open-label, long-term trial to assess safety and efficacy in OAB/ fesoterodine SR 4, 8, and 12mg doses once daily in the double-blind phase; fesoterodine 4mg and 8mg doses once daily in the open-label phase	**186** (125 new fesoterodine exposures subjects)	Up to 4 years or until commercially available
SP738/Extension of SP583/ multicenter, open-label, long-term safety and efficacy in OAB; fesoterodine 4mg and 8mg doses once-daily	**417** (218 new fesoterodine exposures)	Up to 3 years or until commercially available
SP739/Extension of SP584/ multicenter, open-label, long-term safety and efficacy in OAB; fesoterodine 4mg and 8mg doses once-daily	**473** (158 new fesoterodine exposures)	Up to 3 years or until commercially available
Total	**1076**	**—**

Patients enrolled were treated with fesoterodine 8 mg/day (with the option to decrease to 4mg/day), regardless of the treatment received during the previous double-blind phase (placebo, fesoterodine 4 mg or fesoterodine 8 mg).

Conclusions on efficacy from supportive studies are difficult to draw due to the lack of control and to the high number of drop-outs. At the time of the data cut-off only 665 out of 1144 patients enrolled in OL treatment remained. A randomised placebo-controlled withdrawal study (as recommended on the CHMP guideline) would have been preferable in order to better check possible loss of efficacy.

- Discussion on clinical efficacy

Both pivotal studies (SP583 and SP584) where fesoterodine was tested at fixed dose, demonstrated a statistically significant reduction in the principal variables (number of micturitions in 24 hours, 'treatment response'). For the variable "treatment response" both fesoterodine 4mg (63; 74%) and fesoterodine 8mg (74; 79%) doses showed a statistically significant improvement over placebo (45-53%) at end of treatment, implying that a number of patients can expect benefit from the treatment. However, it is difficult to draw firm conclusions on the patient perceived quality of treatment based on the scales used.

Globally considered, the effect of fesoterodine has consistently shown to be superior to placebo.
The magnitude of the treatment effect is modest and the placebo effect is large, especially the treatment difference for the fesoterodine 4 mg dose is rather small. Importantly however, the effect has been demonstrated to be about the same magnitude as for an acceptable comparator.

It is not possible to assess whether there is a clinically relevant treatment effect after 2 weeks treatment. The full treatment effect appears to be observed between 2 to 8 weeks post-treatment. This is reflected in the SPC (section 4.2).

The results in secondary endpoints support the result for primary endpoint and indicate that there is a clinically relevant treatment difference between active and placebo groups.

Most symptoms-related secondary variables also showed statistically significant difference from the baseline after 12 weeks treatment, with numerically better results for highest dose (8 mg/day).

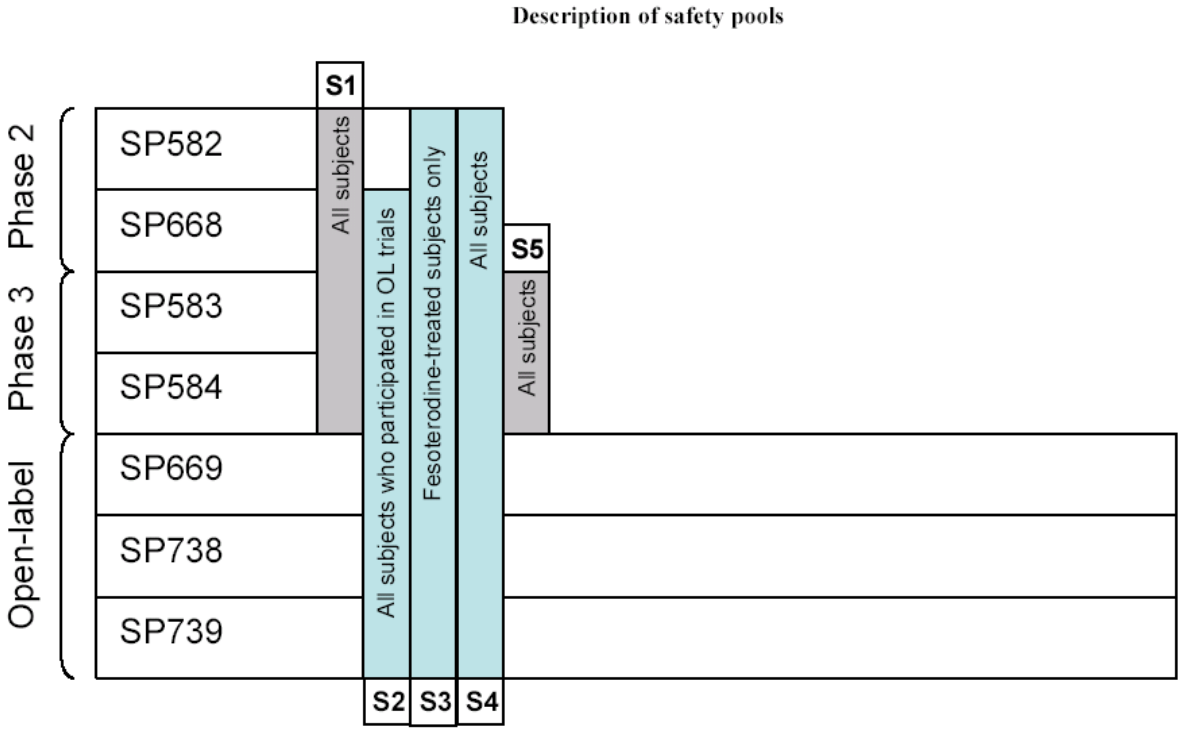
As key secondary endpoints, HRQoL scales were used: KHQ (King's Health Questionnaire) and ICQ-SF (Incontinence Questionnaire- Short Form) both of them standard for these type of studies.

A small but consistent effect on quality of life as assessed by the King's Health Questionnaire in the fesoterodine was shown in pivotal trials. This is a disease-specific health-related validated questionnaire generally used.

As with other drugs intended for the same condition the remaining question is how this results can be translates into a perceivable benefit for the patient.

Clinical safety

Five safety pools have been provided to assess fesoterodine safety (Pool S1, Pool S2, Pool S3, Pool S4 and Pool S5).



In addition, an analysis pool *(Pool P1)* has been used to assess demographic and drug exposure for subjects participating in Phase I trials.

Since the results from the different safety pools can be regarded as fully consistent, the assessment has mainly focussed on pools S1 and S2, which are thought to provide a detailed description of the short and long term safety profiles of fesoterodine

- Patient exposure

Overall, 2859 patients were included in double blind controlled clinical trials, of whom, 780 received placebo, 290 tolterodine and 1789 were treated with fesoterodine (782 with 4 mg/d; 785 with 8 mg/day and 222 with 12 mg/day). The double blind phase of these studies was in most cases 12 weeks.

One thousand and fifty five patients entered the open label extensions from controlled trials, all of them being initially treated with 8 mg/day of fesoterodine. Mean treatment duration was 13.5 months (including the 8-12 week double blind phase). During OL period 20% (206/1055) subjects reduced the dose from fesoterodine 8mg/day to 4mg/day. Among these 173/1055 (16%) remained on 4mg/day and 33/1055 (3%) were again up titrated to 8mg/day.

Regarding the subject disposition within the different safety pools, the following should be considered

In pool S1, overall, 2859 subjects were treated with trial medication. Of these, 442 (16%) discontinued trial medication prematurely. The primary reasons for discontinuation of trial medication were AE (5%), withdrawal of consent (3%), and protocol violation (3%).

Of the 1055 subjects included in *Pool S2 (OL only),* 390 (37%) discontinued treatment prematurely. The most common reasons for discontinuation of OL treatment in Pool S2 were adverse event (117/1055: 11%), withdrawal of consent (99/1055: 9%), and lack of efficacy (97/1055: 9%).

- Adverse events

Adverse events from primary safety trials

Overall, in Pool S1, AEs from any system organ class were reported by 50% of subjects in the placebo (390/780) and tolterodine 4mg/day (144/290) groups, and by 60% (465/782), 64% (500/785) and 73% (163/222) of subjects in the fesoterodine 4, 8, and 12mg/day groups, respectively.

Common adverse events:

The following table provided the treatment-emergent AEs reported by ≥2% of subjects in any fesoterodine group in Pool S1 (sorted in descending frequency by fesoterodine 8mg/day, then fesoterodine 4mg/day, then placebo).

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

Data source: SCS Table 19.1

For the majority of adverse events the occurrence rate was equal to or less than placebo at 4 mg and 8 mg fesoterodine, the doses approved for clinical use, and more common than placebo at the higher 12 mg fesoterodine dose not intended for clinical use. A dose-dependent increase in dry mouth and dry throat were observed in the fesoterodine treatment groups.

Except for urinary tract infection (UTI), back pain, and upper respiratory tract infection, AEs were reported more often in the fesoterodine 12mg/day than in the fesoterodine 4 or 8mg/day treatment groups.

Subjects with urinary retention were considered in 6 (<1%), 8 (<1%), and 3 (1%) subjects in the fesoterodine 4, 8, and 12mg/day groups, respectively. There were no cases of urinary retention in the tolterodine 4mg/day group, and a single case in the placebo group. Residual urine volume and micturition disorder were reported each in 1 (<1%) and 2 (<1%) subjects in the fesoterodine 4, and

12mg/day groups and three subjects reported residual urine volume in the fesoterodine 8mg/day group. No subjects reported residual urine volume and micturition for placebo and tolterodine groups. In addition, no subjects reported micturition disorder fesoterodine 8mg/day. (see *residual urine* and *safety in special population* sections).

Of the subjects reporting AEs during double-blind treatment *in Pool S1*, 121/381 (32%) subjects in the placebo group, 161/458 (35%) subjects in the fesoterodine 4mg/day group, 193/489 (39%) subjects in the fesoterodine 8mg/day group, 66/163 (40%) subjects in the fesoterodine 12mg/day group, and 49/139 (35%) subjects in the tolterodine 4mg/day group had ongoing AEs at the end of treatment.

Adverse events from long-term safety data – Pool S2

Overall, in Pool S2 (DB+OL), AEs from any system organ class were reported by 80% (843/1055) of subjects in total. For OL only, AEs were reported by 70% (734/1055) of subjects.

Common adverse events:

The table below shows the treatment emergent adverse events reported by ≥2% of subjects (Pool S2), sorted in descending order by DB+OL first, then by OL only.

Treatment-emergent adverse events reported by ≥2% of subjects (Pool S2)

Preferred term	DB+OL N=1055 n (%)	OL only N=1055 n (%)
Dry mouth	433 (41)	296 (28)
Urinary tract infection	111 (11)	90 (9)
Constipation	90 (9)	57 (5)
Headache	65 (6)	48 (5)
Diarrhea	47 (5)	33 (3)
Nasopharyngitis	44 (4)	27 (3)
Cough	39 (4)	25 (2)
Nausea	36 (3)	28 (3)
Lacrimal disorder (dry eye)	35 (3)	21 (2)
Upper respiratory tract infection	35 (3)	24 (2)
Back pain	34 (3)	26 (3)
Influenza	34 (3)	26 (3)
Dysuria	33 (3)	21 (2)
Dyspepsia	31 (3)	22 (2)
Gastroesophageal reflux disease	30 (3)	26 (3)
Sinusitis	29 (3)	20 (2)
Dizziness	29 (3)	20 (2)
Urinary retention	28 (3)	25 (2)
Dry throat	27 (3)	15 (1)
Hypertension	24 (2)	18 (2)
Abdominal pain	23 (2)	18 (2)
Bronchitis	23 (2)	17 (2)

DB=double-blind, OL=open-label

Note: Note: This table is sorted in descending order by DB+OL first, then by OL only.

Data source: SCS Table 19.2

Adverse events reported by ≥2% of subjects in Pool S2 were similar to those seen in Pool S1, with the exception of abdominal pain upper, asthenia, chest pain, dysgeusia, vision blurred, and nasal dryness which did not meet the ≥2% criteria, and the addition of urinary retention, gastroesophageal reflux disease, sinusitis, hypertension, and bronchitis, which did meet the ≥2% criteria for inclusion. Typical antimuscarinic AEs such as dry mouth occur early during treatment and are therefore included in the double-blind part of Pool S2. In addition, the DB+OL data in Pool S2 also contains data from SP668, which included the fesoterodine 12mg/day dose.

Onset of drug-associated adverse events

The majority of drug-associated AE had an onset occurring during the first month of treatment, with the frequency of new onset declining over time. However this was not true for urinary retention and gamma glutamyltransferase (GGT) increase which did not show a clear pattern, with onset occurred after month 1. This reflected in the SPC (section 4.8).

Drug related adverse events
Adverse events were considered to be drug related if causality was assessed by the investigator as highly probable, probable, possible or not assessable.

In Pool S1 23%, 33%, 47% and 65% of subjects in placebo, fesoterodine 4, 8, and 12mg/day groups respectively had AEs considered by the investigator to be drug-related. In the tolterodine 4mg/day group, 30% of subjects had an AE considered by the investigator to be drug related.

Adverse events assessed as drug related by investigator occurring in ≥5% 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)	272 (35)	113 (51)	48 (17)
Constipation	16 (2)	26 (3)	40 (5)	18 (8)	7 (2)
Headache	39 (5)	32 (4)	27 (3)	26 (12)	10 (3)
Dry throat	3 (<1)	8 (1)	16 (2)	14 (6)	3 (1)

The most common AEs considered to be drug related correspond well to the pattern for the most common reported AEs known for anticholinergic drug

- Serious adverse event/deaths/other significant events

In pool S1 (all subjects who participated in phase 2 and 3 trials SP582, SP668, SP583, SP584) serious adverse events were reported by 2% placebo treated subjects, 4%, 3% and 6% of subjects treated with fesoterodine 4, 8 and 12mg/day, respectively and by 2% of subjects treated with tolterodine 4mg/day. In all treatment groups, SAEs occurred across multiple body system with no obvious trends.

Serious adverse events reported by >1 subject in any 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 (%)
Pneumonia	1 (<1)	0	2 (<1)	0	0
ECG QT corrected interval prolonged	0	0	2 (<1)	0	0
Chest pain	0	3 (<1)	0	0	0
Appendicitis	0	2 (<1)	0	0	0
Salpingitis	0	2 (<1)	0	0	0

In Pool S3 (fesoterodine treated subjects only who participated in phase 2, phase 3 and open-label trials) serious adverse events were reported in 7%. Myocardial infarction were reported by 7 subjects, angina pectoris and chest pain by 5 subjects each, bronchitis and pneumonia by 4 subjects each and abdominal pain, ECG QT prolongation, QTc interval prolonged were reported by 3 subjects each.

Hepatobiliary disorders
Less than 1% of subjects in any treatment group had hepatobiliary system disorder during treatment, aside from isolated cases of transaminase elevations. Three subjects in Pool S1 had hepatobiliary disorders that were SAE and led to treatment discontinuation. One case of hepato-cellular damage was considered highly related to fesoterodine treatment (8 mg) by the investigator.

Death
Five subjects died during the clinical program for fesoterodine and all were considered to be unrelated to fesoterodine treatment.

- Laboratory findings

In the results for laboratory testing there were individual cases that exceeded the normal range for individual laboratory parameters but overall, there were no clinically relevant trends or change from Baseline to end of treatment in mean values for any haematology, chemistry or urinalysis parameter in any of the treatment groups.

Gamma-GT increase was the only hepatic lab value that met the criteria to be considered drug associated e.g. had an incidence rate of at least 1% and occurring at least twice as often in any of the fesoterodine groups in comparison with the placebo group.

Examination of individual clinically-relevant laboratory abnormalities showed that there was no clinically relevant pattern of laboratory abnormalities reported as AEs, AEs leading to withdrawal or SAE.

- Urinary retention

Mean residual urine volume was influenced somewhat by gender, with small dose-dependent increases in both sexes, but this increase was more pronounced in men.

Increase in mean residual urine were also larger in subjects $\geq$65 and $\geq$75 years of age, than younger subjects.

Discontinuation due to Urinary retention: most cases of urinary retention were mild to moderate in intensity. A post-baseline residual urine volume >200 ml was a protocol defined criterion for discontinuation and discontinued subjects were usually reported as adverse event which coded to urinary retention.Urinary retention led to treatment discontinuation in 3 (<1%), 5 (<1%), and 2 (<1%) subjects in the fesoterodine 4, 8 and 12 mg group respectively. There were no cases of urinary retention in the tolterodine 4mg/day group.

For the overall study population mean change from baseline in residual urine volume was rather small. However there were a number of cases reported with residual urine greater than 200 mL which is considered highly clinically relevant. The results in the safety database indicate that urinary retention is slightly more pronounced in male subjects. This is mentioned in the SPC section 4.8.

- Vital signs and neurological observations

Individual clinically relevant vital sign abnormalities show slight dose-dependent trends in the fesoterodine treatment groups in the proportion of subjects with increases in pulse rate, while the proportions of subjects with changes in blood pressure were similar across treatment groups.
This finding is compatible with the antimuscarinic activity of fesoterodine.

The cognitive function was not specifically tested. With the exception of dizziness, the overall incidence of neurological adverse events was very low; amnesia, confusional state, and disorientation occurred in very few subjects. The incidence of adverse events related to cognitive function in phase 2/3 trials are similar between fesoterodine and placebo treatment. In pool S1 the reported incidence related to cognitive function in the tolterodine group is lower compared to both fesoterodine and

placebo. However, psychiatric disorders (confusion, hallucination) and nervous system disorders (dizziness and somnolence) are known antimuscarinic class effects.

To further support the safety of fesoterodine with respect to cognitive function, a specific Pharmacovigilance plan action is included in the Risk management plan.

- Cardiac safety

Study SP686 (QT/QTc trial)

Methods
The effect of fesoterodine 4 mg and 28 mg/day on the QT interval was evaluated in a phase 1, double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400mg/day) parallel group trial with once-daily treatment over a period of 3 days in 261 healthy male and female subjects aged 44 to 65 years.

Fesoterodine 28 mg/day was chosen because this dose results in an exposure to the active metabolite of fesoterodine that is higher than the exposure in poor CYP2D6 metabolizer receiving fesoterodine 8 mg/day together with a maximum CYP3A4 blockade.

The primary objective 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 concentration and QTcF were examined.
Eletrocardiographic parameters were measured over a 24-hour period at pre-dose, after the first administration, and after the third administration of study medication.

The primary endpoint was the following**:**
Change from baseline in QTc based on Fridericia (**QTcF**) correction method.

Secondary endpoints were the following**:**
Electrocardiograms: change from Baseline in QTc based on individual (**QTcI**) and Bazett (**QTcB**) correction methods. Further secondary endpoint was change from Baseline in heart rate, PR interval, QRS interval, ECG morphological pattern and uncorrected QT interval
Pharmacodynamics: Correction between the QTcF, change in QTcF, and plasma concentration of SPM 7605 (the active metabolite of fesoterodine)

Results
ECG parameters were similar across treatment groups. The exception was for heart rate in which the number of subjects with an 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.

Summary of subjects with a change from baseline

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

Electrocardiograms analysis in Phase 2 and Phase 3 trials

The measurements were captured in a similar way in all Phase 2 and 3 trials using a central ECG facility.

The following table shows ECG findings over time for primary safety trials (*Pools S1 and S5*).

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

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

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

a. For PR interval in the placebo, fesoterodine 4mg/day, fesoterodine 8mg/day, fesoterodine 12mg/day, and tolterodine 4mg/day groups, the number of subjects at EOT were 764, 770, 767, 215, and 282, respectively.

b. For PR interval in the placebo, fesoterodine 4mg/day, fesoterodine 8mg/day, and tolterodine 4mg/day groups, the numbers of subjects at EOT were 541, 544, 552, and 282, respectively.

Data source: SCS Table 68.1 and SCS Table 72.1

At the end of treatment in Pool S1, marginal mean increases (3-6bpm) in heart rate, consistent with the observed slight increase in pulse rate, were observed in subjects receiving fesoterodine and tolterodine compared with a mean increase of <1bpm in the placebo group. Increased heart rate is a known pharmacological effect of antimuscarinic drugs.

Individual changes in QTc were classified as observed values <450ms, 450 to <480ms, 480 to <500ms, and ≥500ms. Changes from Baseline were classified as <30ms, 30 to <60ms, and ≥60ms.

The following table summarizes change from Baseline at end of treatment in QTcF and QTcB results for Pool S1.

Change from Baseline at end of treatment in QTcF and QTcB results (Pool S1 and Pool S5)

QTc(F and B)	Placebo n (%)	Feso 4mg/day n (%)	Feso 8mg/day n (%)	Feso 12mg/day n (%)	Tolt 4mg/day n (%)
Pool S1 (at EOT)	**N=768**	**N=774**	**N=772**	**N=216**	**N=285**
<30ms: QTcF	739 (96)	748 (97)	747 (97)	209 (97)	277 (97)
QTcB	719 (94)	710 (92)	708 (92)	198 (92)	260 (91)
30-<60ms: QTcF	27 (4)	26 (3)	23 (3)	7 (3)	8 (3)
QTcB	43 (6)	62 (8)	61 (8)	16 (7)	24 (8)
≥60ms: QTcF	2 (<1)	0	1 (<1)	0	0
QTcB	6 (<1)	2 (<1)	2 (<1)	2 (<1)	1 (<1)
Pool S5 (at EOT)	**N=545**	**N=546**	**N=557**	--	**N=285**
<30ms: QTcF	524 (96)	531 (97)	535 (96)		277 (97)
QTcB	512 (94)	500 (92)	505 (91)	--	260 (91)
30-<60ms: QTcF	20 (4)	15 (3)	20 (4)		8 (3)
QTcB	30 (6)	46 (8)	49 (9)	--	24 (8)
≥60ms: QTcF	1 (<1)	0	1 (<1)		0
QTcB	3 (<1)	0	2 (<1)	--	1 (<1)

EOT=end of treatment; Feso=fesoterodine, Tolt=tolterodine

NOTE: QTcF and QTcB were missing for 1 subject in the fesoterodine 8mg/day group in Pool S1 and Pool S5.

Data source: SCS Table 80.1, SCS Table 82.1, SCS Table 83.1, SCS Table 85.1

Change from Baseline ≥30ms in QTcF and QTcB at the end of treatment was generally similar across the treatment groups in both Pool S1 and Pool S5. At end of treatment in Pool S1, 1 subject in the fesoterodine 8mg/day group had a ≥60ms change from Baseline in QTcF and 2 subjects in each fesoterodine treatment group had a ≥60ms change from Baseline in QTcB. Similar results were seen in Pool S5 except that there were no QTcB changes ≥60ms in the fesoterodine 4mg/day group. There was no indication of an increased incidence of QTc prolongation with increased exposure to fesoterodine over a 3-month period calculated by either formula.

Overall, change from Baseline in QTc based on the Fridericia correction method did not show any differences between the active treatment and placebo group. Since, QT prolongation was also seen in >5 subjects in the safety file for fesoterodine, the possibility of an increased risk for QT prolongation, associated with fesoterodine treatment, cannot be excluded. Therefore, as with other antimuscarinics, caution is given in the SPC (section 4.4) for patients with risk for QT-prolongation (e.g. hypokalaemia, bradycardia and concomitant administration of medicines known to prolong QT interval) and relevant pre-existing cardiac diseases (e.g. myocardial ischaemia, arrhythmia, congestive heart failure).

- Safety in special populations

Safety by gender and age

In the treated study population 32% were older than 65 years and 9% were older than 75 years. Approximately 19 % of the treated study population was men. Mean treatment duration was comparable in each treatment group regardless of gender.

There were some difference in AE pattern based on age, with constipation, urinary tract infection and dizziness occurring more often in older (≥65 years and ≥75 years) subjects. Dry mouth was more frequent in the fesoterodine 8mg/day group among subjects ≥75 years old than in those <75 (45% vs. 34%, respectively). Headache was more common in younger subjects.

Gender appeared to play a role in the frequency of some AEs including dry mouth which occurred more often in females.

Safety in poor metabolizers for CYP2D6
Poor metabolizers for CYP2D6 were more likely than extensive metabolizers to experience AEs such as those known to be associated with antimuscarinic treatment. This effect was more pronounced in the fesoterodine 8mg/day group, eg, constipation, dry mouth, dry eye, residual urine retention and dyspepsia occurred more often in poor metabolizers.

Regarding residual urine, results showed that there was a greater mean increase in poor metabolizers than extensive metabolizers. The most pronounced difference was in the fesoterodine 8mg/day group where mean increase in residual urine was 24mL in poor metabilizers and 14mL in extensive metabolizers.

- Safety related to drug-drug interactions and other interactions

Concomitant use of CYP3A4 inhibitors did appear to influence the occurrence of some AEs, particularly dry mouth, constipation, and dry throat which were reported more frequently by subjects who used CYP3A4 inhibitors than those who did not use them, and more often in each fesoterodine group than in the placebo group. During open-label treatment dry mouth occurred with similar incidence in subjects who did not use CYP3A4 inhibitors, and those who did.

- Discontinuation due to adverse events

A total of 142 subjects in *Pool S1* discontinued due to AEs during treatment: 26/780 (3%) in the placebo group, 35/782 (5%), 45/785 (6%), and 27/222 (12%) subjects in the fesoterodine 4, 8, and 12mg/day groups, respectively, and in 9/290 (3%) subjects in the tolterodine 4mg/day group.

Other than dry mouth, there was no clear dose-dependent relationship between fesoterodine dose and frequency of discontinuations due to any particular AE.

Adverse events led to *discontinuation* of fesoterodine in 11% of subjects during long-term treatment *(Pool S2)*, and were typical of those seen during treatment with antimuscarinics. These included (in more than 2 subjects during open-label treatment) dry mouth in 16 (2%) subjects, urinary retention in 10 (<1%) subjects, constipation in 8 (<1%) subjects, residual urine volume in 6 (<1%) subjects, lacrimal disorder (dry eye) in 5 (<1%) subjects, and urinary tract infection, cough, dry throat, and dry skin in 3 (<1%) subjects each. This AE dropout profile is similar to that in Pool S1 with the addition of cough, dry skin, and residual urine volume (6 subjects, <1%) in Pool S2.

Overall 12% of subjects in *Pool S2* had their *dose reduced* from 8mg to 4mg during open-label treatment due to a treatment-emergent adverse event. Dry mouth in 91/1055 (9%) subjects was the AE most often leading to dose reduction during OL treatment. This was followed by dysuria and constipation, leading to dose reduction in 8 (<1%) subjects each, lacrimal disorder (dry eye) in 7 (<1%) subjects, headache in 6 (<1%) subjects, dry skin in 4 (<1%) subjects, and urinary hesitation and dry throat in 3 (<1%) subjects each. The majority of dose reductions occurred during the first 6 weeks of treatment.

- Post marketing experience

Not applicable.

- Discussion on clinical safety

Common AEs (Treatment Emergent AEs (TEAEs) with incidence rate of at least 2% in any fesoterodine group) that occurred more often in subjects treated with fesoterodine 4 and 8mg/day than placebo included (in descending order based on the 4mg/day dose of fesoterodine) dry mouth 22% (173/782), headache 8% (64/782); constipation 4% (28/782), nasopharyngitis 4% (28/782), urinary tract infection 3% (26/782), dyspepsia 2% (12/782), nausea 2% (17/782), dysuria 2% (12/782), and back pain 2% (19/782).

The AEs profile for the 8 mg/d dose was similar to the above described with a numerically higher incidence of dry mouth (35%). Except for urinary tract infection, nasopharyngitis, and back pain, these AEs were reported more often in the fesoterodine 12mg/day than in the fesoterodine 4 or 8mg/day treatment groups. The AEs profile for tolterodine was similar to the observed for the 4 mg/day of fesoterodine, with a numerically lower incidence of dry mouth and headache.

During the open label (OL) extensions (Pool S2) the profile of common AEs was generally similar to that listed above for Pool S1 (double blind treatment).

Most AEs were mild or moderate in intensity in Pool S1, and Pool S2 for both analyses. In Pool S1, severe AEs were reported for 4% (29/780), 5% (41/782), 8% (61/785), 14% (30/222), and 3% (8/290) of subjects in the placebo; fesoterodine 4, 8, and 12mg/day groups; and tolterodine 4mg/day group, respectively. Dry mouth was the AE most often rated as severe in intensity (<1%, <1%, 3%, 9%, and 0 in placebo; fesoterodine 4, 8, and 12mg/day; and tolterodine 4mg/day group, respectively). Dry throat, lacrimal disorders and headache were also reported as severe AEs in ≥1% subjects in the fesoterodine 12mg group.

Drug-associated AEs were reported for any system organ class (SOC) by 23% (176/780) of subjects in the placebo group, 35% (271/782), 46% (359/785), and 64% (141/222) of subjects in the fesoterodine 4, 8, and 12mg/day groups, and 29% (84/290) of subjects in the tolterodine 4mg/day group, respectively. Drug associated adverse events reported in ≥2% (in descending order based on incidence of adverse events in fesoterodine 8mg/day, followed by fesoterodine 4mg/day, followed by placebo) were dry mouth, constipation, dyspepsia, lachrymal disorder (dry eye), dry throat, dysuria, abdominal pain upper and back pain.

First onset of drug associated adverse events occurred mostly during Month 1 of treatment, decreasing the incidence afterward. Urinary retention and GGT increased did not show the same pattern of onset.

In Pool S1, a total of 142/2859 (5%) subjects discontinued clinical trials due to AEs (3% in the placebo group, 5%, 6%, and 12% in the fesoterodine 4, 8, and 12mg/day groups, respectively, and 3% subjects in the tolterodine 4mg/day group). During long-term treatment, adverse events led to discontinuation of fesoterodine in 11% of subjects. Reasons for discontinuations (each of them accounting for less than 1%) were dry mouth, urinary retention, constipation, ECG corrected interval prolonged, GGT increased, mucosal dryness, headache, dyspepsia, dry throat, nausea, vertigo, dizziness, chest pain, lacrimal disorder, vomiting and vision blurred. There was a clear dose-dependent relationship between fesoterodine dose and frequency of discontinuations due to dry mouth rising to 5% in the fesoterodine 12mg/day group. No other AE showed such a clear dose dependence relationship.

Twelve percent (12%) of subjects had their dose reduced from 8mg to 4mg during open-label treatment due to TEAE. Dry mouth in 91/1055 (9%) subjects was the AE most often leading to dose reduction during OL treatment. The majority of dose reductions occurred during the first 6 weeks of treatment.

Serious Adverse Events (SAE) were reported in Pool S1 by 2% placebo (15/780) and tolterodine (7/290) treated subjects, 27/782 (4%), 23/785 (3%), and 13/222 (6%) subjects treated with fesoterodine 4, 8, and 12mg/day, respectively. During open-label treatment, SAEs were reported by 92/1055 (9%) subjects treated with fesoterodine.

SAEs reported by more than 2 fesoterodine treated subjects included myocardial infarction reported by 7 subjects, angina pectoris and chest pain by 5 subjects each, bronchitis and pneumonia, each reported by 4 subjects, and abdominal pain, ECG QT corrected interval prolonged, invertebral disc protrusion, breast cancer, appendicitis, and cholecystectomy reported by 3 subjects each (all <1%).

Seventeen 17/1055 (2%) subjects discontinued treatment due to SAE during OL. None of the SAEs reported in Pool S2 OL only, led to discontinuation in more than 1 subject.

A thorough QT study in healthy volunteers was conducted. Fesoterodine up to 28 mg/d for 3 days was assessed. A placebo and positive control (moxifloxacine) arms were included. The results did not show fesoterodine to have an effect on the QT surpassing the established threshold of regulatory concern (10 msec). These findings have been properly reflected in the SPC
.
These results are apparently confirmed by the ECG analysis from therapeutic trials, although 3 subjects assigned to fesoterodine 4mg/day and 6 to fesoterodine 8 mg discontinued the study drug due to QT prolongations. Importantly, 3 patients on the 8 mg dose were reported to have a SAE related to QT prolongation. Further analysis revealed that the incidence rates of QTc >=500 ms post-baseline or QTc increase of >=60 ms (some of which were classified as SAEs), were similar in active and placebo groups: 1.9%, 1.3%, 1.4% and 1.5% for fesoterodine 4 mg, 8 mg, 12 mg and placebo, respectively.

Mean changes from Baseline in residual urine volume were usually greater in males than in females and greater in older subjects (≥65 years and ≥75 years) compared with younger subjects (<65 years and <75 years). A dose dependent increase in residual urine volume was observed in the fesoterodine treatment groups. Although urinary retention is compatible with the antimuscarinic activity, results showed a numerically higher incidence amongst the fesoterodine treated patients than tolterodine treated patients.

Cognitive function is known to be possibly affected by antimuscarinic agents. With increasing incidence of urge incontinence with age, elderly patients are a relevant target population. Although the incidence of adverse events related to cognitive function was low and not different from placebo, a specific pharmacovigilance plan action is included in the risk management plan.

During the extension clinical trials, patients were down-titrated and up-titrated accordingly, apparently, with their tolerability to treatment. Moreover, there were a 3% of subjects who were up-titrated again to the 8mg/day dosage.

No relevant laboratory abnormalities has been reported for fesoterodine apart from isolated cases of raised liver enzymes determinations, in some cases leading to treatment discontinuation.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements

Risk Management Plan

The MAA submitted a risk management plan.

Summary of the Risk Management Plan and Risk Minimization Plan for fesoterodine

Safety concern	Proposed pharmacovigilance activities	Milestones	Proposed risk minimization activities
Limited information			
Elderly male patients	Routine pharmacovigilance Cumulative summary by age and gender in Periodic Safety Update Reports (PSURs)	PSUR	see SPC Section 4.4
Paediatric patients	Routine pharmacovigilance, PSURs	PSUR	see SPC Sections 4.2 and 5.2
	Enhanced Pharmacovigilance Paediatric Development Plan	available in 2007	
Pregnant or nursing women	Routine pharmacovigilance, PSURs	PSUR	see SPC Sections 4.6 and 5.3
Potential safety risks			
QT prolongation	Enhanced pharmacovigilance with systematic reviews in PSURs	PSUR	see SPC Sections 4.8, 5.1, 5.3
Liver enzyme elevations	Enhanced pharmacovigilance with systematic reviews in PSURs	PSUR	see SPC Sections 4.8 and in 4.2, 4.3, 4.4, 5.2
Urinary retention	Enhanced pharmacovigilance with systematic reviews in PSURs	PSUR	see SPC Sections 4.5 and 4.8
Cognitive function	Routine pharmacovigilance with cumulative summary by age and gender in PSURs	PSUR	see SPC Section 4.7

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information. The specific areas of monitoring for safety concerns are those mentioned in the above table.

In summary, routine and enhanced pharmacovigilance will be employed. The applicant will provide reviews of AEs associated with the use of fesoterodine, as well as specific reviews of QT prolongation/Torsades de Pointes, hepatic disorders, urinary retention, cognitive function impairment, and systematic analysis by age and gender of AEs.

A paediatric development program is being designed and will be submitted and the Agency will be informed of the relative studies.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
There are no unresolved quality issues which may affect the Benefit/Risk balance.

Non-clinical pharmacology and toxicology

Pharmacotoxicological studies have shown effects in relation to the antimuscarinic activity of fesoterodine and its main metabolite (SPM 7605).

Fesoterodine and SPM 7605 induced a concentration-dependent inhibition of hERG current with IC_{50} values of 3.6 and 0.5 µM, respectively. However in conscious dogs, the active metabolite had no effect on the QT interval and QTc interval at plasma exposures more than 20-fold higher than the mean peak free plasma concentration in humans.

The main target organ of toxicity was the liver in rats. No target organ of toxicity was identified in the mouse or the dog.

Fesoterodine is non-genotoxic and non-carcinogenic

.

Reproduction studies have shown minor embryotoxicity at doses close to maternally toxic ones (increased number of resorptions, pre-implantation and post-implantation losses).

Environmental studies including chronic ecotoxicity tests of the active metabolite SPM 7605 in aquatic organisms of at least three trophic levels, are ongoing and will be completed in the post-authorisation phase. (Follow-up measure)

Efficacy

The demonstration of the clinical efficacy of fesoterodine is based on 2 pivotal trials in which the doses of 4 and 8 mg/d have been compared to placebo and tolterodine. The clinical efficacy results are statistically significantly superior to placebo in all primary endpoints i.e. reduction in the number of micturitions per 24 hours, of urge incontinence episodes per 24 hours and improvement of the treatment response rate using a treatment benefit scale.

The efficacy results for fesoterodine 4mg/day and the active comparator tolterodine are judged comparable whereas the efficacy for fesoterodine 8mg/day was more pronounced.

For the overall patient group, the clinical relevance for the efficacy differences between the different doses of fesoterodine is difficult to assess, but the slightly better treatment effect of the higher dose of 8mg/day, may imply some benefit for the individual patient.

Therefore, it can be concluded that the efficacy of fesoterodine in overactive bladder syndrome, though modest, has been reasonably and consistently established both against placebo and an acceptable active comparator with a similar mechanism of action.

Safety

The safety profile of fesoterodine is the one expected for an antimuscarinic drug. No major safety concerns have been identified, although a numerically higher incidence and severity of some anticholinergic AEs as compared with tolterodine were observed.

No evidence from a QT prolonging effect is apparent from either a specific QT study or in depth ECG analysis from phase II and III data. However, some QT-related AEs have been reported, especially for the 8 mg dose. This is reflected in the SPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities adequately addressed these.

- User consultation

The readability of the package leaflet for fesoterodine was tested based on the method for user testing described in the Readability Guideline. The outcome was satisfactory in accordance with predefined success criteria.

Risk-benefit assessment

The demonstration of the clinical efficacy of fesoterodine is based on 2 pivotal trials in which the doses of 4 and 8 mg/d have been compared to placebo and tolterodine. Globally considered, the effect of fesoterodine has been consistently shown to be superior to placebo. Importantly, the magnitude of such effect has been demonstrated to be about the same magnitude of an acceptable comparator. For the overall patient group, the clinical relevance for the efficacy differences between the different doses of fesoterodine is difficult to assess, but the slightly better treatment effect of the higher dose of 8mg/day, may imply some benefit for the individual patient. Therefore, and fully recognising the above mentioned limitations, the efficacy of fesoterodine in the intended indication can be considered as reasonably established.

Fesoterodine presents a clinical safety profile fully compatible with its antimuscarinic activity. There was an evident dose relationship for the incidence of some clinical AEs, with a slightly numerically higher incidence amongst fesoterodine 4 and 8 mg treated patients than with tolterodine. No outstanding safety concerns are apparent from the assessment of submitted data.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
  Safety issues have been properly taken into consideration in the revised risk management plan: cardiovascular safety, liver toxicity, urinary retention and cognitive function impairment.

- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of TOVIAZ (fesoterodine) in "Treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome" was favourable and therefore recommended the granting of the marketing authorisation.