# CLINICAL PROTOCOL

## A 24-WEEK RANDOMIZED, OPEN-LABEL, STUDY TO EVALUATE THE SAFETY AND EFFICACY OF FESOTERODINE IN SUBJECTS AGED 6 TO 17 YEARS WITH SYMPTOMS OF DETRUSOR OVERACTIVITY ASSOCIATED WITH A NEUROLOGICAL CONDITION (NEUROGENIC DETRUSOR OVERACTIVITY)

| | |
|---|---|
| **Compound:** | PF-00695838 |
| **Compound Name (if applicable):** | Fesoterodine |
| **US IND Number (if applicable):** | [redacted] |
| **European Clinical Trial Database (EudraCT) Number:** | 2010-022475-55 |
| **Protocol Number:** | A0221047 |
| **Phase:** | 3 |

[redacted]

The name, title, address and telephone numbers of the sponsor's medical expert for the trial is documented in the study contact list located on the web portal, (www.epharmasolutions.com/2326.html).

[redacted]

## Document History

| Document | Version Date | Summary of Changes |
|---|---|---|
| Amendment 5 | 3 March 2014 | • To enroll subjects ≤25 kg as a separate cohort within the study who will be administered a beads-in-capsule (BIC) formulation.<br>• To specify a target of approximately 99 evaluable subjects at Week 12 for subjects > 25 kg.<br>• To include the enrollment of subjects aged 17 years old.<br>• To correct minor errors and update with current protocol template. |
| Amendment 4 | 02 October 2012<br>Country-specific: France<br>(See Appendix 5) | The additional wording for the exclusion criteria are:<br>• The protocol will exclude patients who have had an endoscopic anti-reflux therapy in the previous 3 months before Visit 2.<br>• Patients who present with QTc interval prolongation, personal and family history of QTc interval prolongation, or pre-existing and important cardiac diseases and present a risk of QT interval Prolongation (eg, hypokalemia) will be excluded. |

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| | | The additional specific withdrawal criterion is:<br>• That an endoscopic anti-reflux therapy during the trial period is a criterion of premature exit from the trial<br>• Minor QC/wording correction. |
| Amendment 3 | 11 January 2012 | Rationale:<br><br>Update to various sections following new SOP CT02 template, implemented 17 November 2011.<br><br>PG sampling for oxybutynin subjects who continue into the safety extension phase.<br><br>Minor QC/wording corrections and updates. |
| Amendment 2 | 07 October 2011 | Rationale:<br><br>Update to Section 15.1 following new SOP CT02 template, implemented 08 September 2011.<br><br>Updates following FDA advice letter, including: Vision testing, cognitive function testing, telephone call for all treatment groups at Week 1, Removal of PinQ, Laboratory evaluations at baseline, Week 12 and Week 24, PK sample collection at Week 4 instead of Week 12.<br><br>Changes to wording for Oxybutynin supply and administration.<br><br>Various minor editorial changes. |

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| Amendment 1 | 27 April 2011 | Rationale:<br><br>The protocol has been updated with the following:<br><br>Updates to SOP CT02 clinical protocol template, implemented 08 November 2010 country feedback on the protocol (eg, acceptability of dose optimization assessments and standards of care) evaluation of risks related to study complexity, operationalizing and executing the protocol, in particular dose titration/optimization of the comparator (oxybutynin) decision to use electronic bladder diary and dosing log.<br><br>Updates made following review by FDA and Pfizer internal Technical Review Committee.<br><br>Administrative QC. |
| Original protocol | 03 August 2010 | N/A |

These amendments incorporate all revisions to date, including amendments made at the request of country Health Authorities, IRB/IEC, etc.

## SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

| Protocol Activity | Visit 1 | Visit 2 | Phone Call all groups [q] | Oxybutynin dose optimization period[a,q] | | Visit 3 | Visit 4[q] | Visit 5[b] | Visit 6[q] | Visit 7[c] | Visit 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Rand | | Phone Calls Oxybutynin subjects | | Feso PK & Fix Oxy dose | Phone call | Start of Extension | Phone Call | End of Treat-ment | Follow-up call |
| | Day -30 to Day -3 | Day 1 | Week 1 | Week 2 | Week 3 | Week 4 | Week 8 | Week 12 | Week 18 | Week 24 | Week 26 |
| Informed Consent & Assent | X | | | | | | | | | | |
| Demography | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Review Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Event Monitoring | | X | X | X | X | X | X | X | X | X | X |
| Electrocardiogram (ECG) | X | | | | | | | | | | |
| Child Behavior Check List (CBCL) | | X | | | | | | X | | X | |
| Grooved Pegboard test | | X | | | | | | X | | X | |
| Vital Signs[d] | X | X | | | | X | | X | | X | |
| Weight | X | | | | | X | | X | | X | |
| Physical Examination[d] | X | | | | | | | X | | X | |
| Visual acuity and accommodation | | X | | | | | | X | | X | |
| Post-void residual (PVR) urine volume[e] | X | X | | | | X | | X | | X | |
| Laboratory[f] | | | | | | | | | | | |
| Hematology | X | | | | | | | X | | X | |
| Blood Chemistry | X | | | | | | | X | | X | |
| Urinalysis[g] | X | | | | | X | | X | | X | |
| Urine/Serum Pregnancy Test[h] | X | X | | | | X | | X | | X | |
| Pharmacokinetics (PK) blood sampling[i] | | | | | | X | | | | | |
| Pharmacogenomics (PG) blood sampling[j] | | | | | | X | | X | | | |
| Urodynamic Studies[k] | | X | | | | | | X | | | |
| Dispense electronic data capture device[l] | X | | | | | | | | | | |
| Collect/review electronic data capture device[m] | | X | | | | X | | X | | X | |
| Bladder diary | | | | | | | | | | | |
| Completion instructions | X | | | | | | | | | | |

| Protocol Activity | Visit 1 | Visit 2 | Phone Call all groups [q] | Oxybutynin dose optimization period[a,q] | | Visit 3 | Visit 4[q] | Visit 5[b] | Visit 6[q] | Visit 7[c] | Visit 8 |
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| | Screening | Rand | | Phone Calls Oxybutynin subjects | | Feso PK & Fix Oxy dose | Phone call | Start of Extension | Phone Call | End of Treat-ment | Follow-up call |
| | Day -30 to Day -3 | Day 1 | Week 1 | Week 2 | Week 3 | Week 4 | Week 8 | Week 12 | Week 18 | Week 24 | Week 26 |
| Completion reminder 1 week before | | X | | | | | | X | | | |
| Review bladder diary[n] | | X | | | | | | X | | | |
| Dosing log | | | | | | | | | | | |
| Completion instructions | | X | | | | | | | | | |
| Review dosing log[n,o] | | | X | X | X | X[p] | X | X[p] | X | X | |
| Study Medication Dispensed | | X | | | | X | | X | | | |
| Study Medication return/count | | | | | | X | | X | | X | |
| Assess Study Medication compliance | | | | | | | | X | | X | |
| Oxybutynin dose adjustment [a] | | | X | X | X | | | | | | |
| Dispense appointment & dosing record card | | X | | | | | | | | | |
| Review and collect appointment & dosing record card | | | | | | | | X | | | |

| Protocol Activity | Visit 1 | Visit 2 | Phone Call all groups [q] | Oxybutynin dose optimization period[a,q] | | Visit 3 | Visit 4[q] | Visit 5[b] | Visit 6[q] | Visit 7[c] | Visit 8 |
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| | Day -30 to Day -3 | Day 1 | Week 1 | Week 2 | Week 3 | Week 4 | Week 8 | Week 12 | Week 18 | Week 24 | Week 26 |

a. Subjects who are receiving oxybutynin (>25 kg subjects) will have additional contacts, by telephone or clinic visits, as deemed appropriate, at approximately weekly intervals for dose adjustment to optimize efficacy and tolerability.
b. Or in the event of the subject withdrawing early from the active comparator treatment/efficacy phase. Urodynamic assessment should only be performed in subjects who have been on a stable dose of study medication for at least 2 weeks, and who have not missed any doses in the 3 days prior to the visit.
c. Or in the event of the subject withdrawing early from the safety extension phase.
d. If vital signs or physical examinations show a clinically relevant change from baseline, then safety monitoring will occur at a minimum of monthly intervals, or more frequently as clinically appropriate, until the abnormality resolves.
e. PVR only in subjects who are not performing intermittent catheterization or in any subjects who have >1 urinary tract infection (UTI) during the study.
f. Laboratory assessments may be repeated as needed to follow-up on significant findings.
g. Urinalysis: Urine microscopy, culture, and sensitivity to be performed in the event of the presence of symptoms (eg, fever, flank pain), positive leucocytes and/or nitrites on urinalysis, or if the subject has a documented history of vesicoureteral reflux (VUR).
h. Serum pregnancy test at Visit 1, urine pregnancy test at all other visits. Only for female subjects of child-bearing potential. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
i. PK blood sampling only in subjects randomized to treatment with fesoterodine during the active comparator/efficacy phase. A maximum of three PK samples will be collected from each subject. Subjects randomized to treatment with oxybutynin (>25 kg subjects) will not be required to provide PK samples. In the event of subject withdrawing early from the active comparator/efficacy phase prior to Visit 3, PK samples should be obtained at the early termination visit.
j. At Visit 3 PG samples only in subjects randomized to treatment with fesoterodine during the active comparator/efficacy phase, and who do not have prior laboratory documentation of their CYP2D6 genotype. At Visit 5 (or early withdrawal from the active comparator/efficacy phase), only subjects (>25 kg) who were on oxybutynin who will continue into the safety extension phase and who do not have prior laboratory documentation of their CYP2D6 genotype.
k. Urodynamic studies: subjects who demonstrate a clinically relevant increased detrusor pressure or other urodynamic findings suggestive of worsening condition compared to baseline should not be allowed to continue into the safety extension phase. Consideration should be given to imaging of upper urinary tract (for example, videourodynamics, or ultrasound) according to accepted local standard of care in subjects with VUR, or other conditions that predispose to upper urinary tract dysfunction or damage.
l. Bladder diary and dosing log data will be recorded on the same electronic data capture device. The bladder diary will be completed for 3 days prior to Visits 2 and 5; the dosing log will be completed on a daily basis. Subjects and/or their caregivers should be re-educated and re-trained if review of data suggests that the bladder diary or dosing log are not being completed correctly.
m. Electronic data capture device should be collected at Visit 2 for subjects who are not randomized, or at other visits if the subject discontinues.
n. Assessment of the bladder diary or dosing log may be performed via remote electronic review.
o. Review of dosing log should occur as indicated and also within 2 - 3 days following initiation in treatment or change in dose, tablet/capsule strength or treatment (oxybutynin) or as otherwise appropriate.
p. At Visit 3, the time of last 3 doses should be recorded for fesoterodine, and at Visit 5 the time of last dose of fesoterodine or oxybutynin.
q. Telephone calls may be substituted by a clinic visit at the discretion of the investigator and when indicated by local circumstances and/or regulatory requirements (eg for Japan, clinic visits should be the default option).

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**APPENDICES**

# 1. INTRODUCTION

## 1.1. Indication

Fesoterodine is an antimuscarinic drug that is being developed for the treatment of symptoms associated with a neurological condition (eg, spina bifida) in subjects aged 6-17 years, hereafter referred to as "neurogenic detrusor overactivity" or NDO.

## 1.2. Background and Rationale

At least 25% of clinical problems seen in pediatric urology are the result of neurogenic lesions that affect lower urinary tract function (Bauer, et al 2002).[1] The principal causes may be classified as acquired or congenital in origin, with the vast majority of bladder dysfunction in children related to neural tube defects, most commonly myelomeningocele (Aslan & Kogan, 2002).[2]

Neurogenic detrusor overactivity is associated with involuntary contractions of the detrusor muscle, defined as detrusor overactivity, which occur as the bladder fills. This can only be diagnosed with cystometric evaluation (Neveus, et al, 2006).[3]

The outcome of upper urinary tract function is related to detrusor and urethral sphincter function. In dyssynergistic dysfunction, detrusor and urethral sphincter contraction is uncoordinated (detrusor-sphincter dyssynergia) resulting in high intravesical pressures, vesicoureteric reflux, and ultimately renal damage (Coward & Saleem, 2001);[4] (Aslan & Kogan, 2002).[2] In children with myelodysplasia, the risk of upper urinary tract (UUT) deterioration and renal damage approaches 80% when no intervention is instituted (Bauer et al, 2002).[1]

In atonic dysfunction, although a lack of detrusor and (usually) sphincter activity results in a low pressure bladder generally protecting the urinary tract, incontinence then becomes a problem (Coward & Saleem, 2001);[4] (Aslan & Kogan, 2002).[2]

Treatment of NDO in children depends on presentation, underlying cause, and the risk of deterioration in function of both upper and lower urinary tract. Clean intermittent catheterization (CIC) is first line therapy for bladder emptying in children with areflexic bladders and high postvoid residual urine volume, and may be combined with antimuscarinic therapy in specific populations, eg, patients with high pressure bladders as below (Aslan & Kogan, 2002);[2] (Kennelly & DeVoe, 2008).[5]

### Drug Development Rationale

Antimuscarinic drugs are the cornerstone of pharmacotherapy in the pediatric NDO population, and have been shown to improve intravesicular pressure, and decrease symptoms. Four antimuscarinic drugs (oxybutynin, trospium chloride, tolterodine and darifenacin) have documented results in the pediatric NDO population (Kennelly & DeVoe, 2008).[5] Of these,

only oxybutynin is widely approved for use in children, and is available as a once a day extended release (XL) tablet, as well as an immediate release tablet. Although effective, oxybutynin use has been limited by a side effect profile which may have particular relevance in the pediatric population where development (eg, physical, cognitive, psychosocial) is still ongoing.

A particular medication's effectiveness is highly dependent on patient compliance which is itself dependent on tolerability. Given individual differences in toleration and the limited choice available there is an unmet need for alternative treatments.

Children with NDO therefore represent a disease population with a need for an alternative effective, safe and well-tolerated therapy to help manage the overactive detrusor, reducing or preventing incontinence, as well as the high pressure bladder contractions that can result in UUT deterioration and renal damage.

Other treatments such as alpha blockers, anxiolytics, tricyclic antidepressants, intravesical oxybutynin, botulinum-A toxin, electrical stimulation and biofeedback, may also be used (Coward & Saleem, 2001)[4] although safety and efficacy have not been reliably demonstrated.

Acetylcholine which interacts with muscarinic receptors at the detrusor is the predominant peripheral neurotransmitter responsible for bladder contraction. Both fesoterodine and oxybutynin are muscarinic receptor antagonists and consequently have a role in mediating detrusor overactivity.

Fesoterodine is an antimuscarinic drug available as a prolonged release (PR) tablet formulation, and is approved in Europe and the USA at doses of 4 mg and 8 mg once daily for the treatment of overactive bladder (OAB) in adults; it is not approved for use in the pediatric population.

Fesoterodine functions as a prodrug of 5-hydroxymethyltolterodine (5-HMT). After oral administration, fesoterodine cannot be detected in plasma, as it is rapidly and extensively hydrolyzed by nonspecific esterases to 5-HMT, which is the principal active moiety responsible for the antimuscarinic effects of fesoterodine.

**Clinical Safety Data**

Adverse effects characteristic of antimuscarinic drugs, eg, dry mouth, constipation, urinary retention, micturition difficulties, dry eyes, and dry throat were observed in Phase 1 studies with fesoterodine doses up to 28 mg once daily. In a double-blind, randomized, parallel-group, placebo- and positive-controlled (moxifloxacin 400 mg/day) thorough QT study with fesoterodine 4 mg and 28 mg/day doses, fesoterodine did not prolong the QTc interval. Fesoterodine PR has been evaluated in Phase 2 and Phase 3 controlled studies in 2859 OAB patients. Of this total, 782 received fesoterodine 4 mg/day and 785 received fesoterodine 8 mg/day for treatment periods of 8 or 12 weeks. The most common adverse event in Phase 3 was dry mouth, with a reported incidence of 19% with fesoterodine 4 mg and 35% with fesoterodine 8 mg, compared to 7% with placebo. Most of the cases were mild to moderate and discontinuations due to dry mouth were less than 1%. Constipation was the second most

common adverse event with a reported incidence of 4% with fesoterodine 4 mg and 6% with fesoterodine 8 mg compared to 2% with placebo. There were no apparent trends in mean changes from baseline to the end of treatment or in shifts of clinical relevance over time in any hematology, clinical chemistry, or urinalysis parameters. Among subjects treated with fesoterodine, no clinically relevant changes from baseline were observed for vital sign parameters, electrocardiogram (ECG) parameters, physical examination findings, or residual urine data. In summary, fesoterodine is generally well-tolerated at doses of 4 mg and 8 mg once daily.

An 8-week open-label, uncontrolled pharmacokinetics and safety study was conducted in 21 pediatric OAB patients, aged between 8-17 years, weighing >25 kg (A0221066). Each subject was to receive the initial study dose of 4 mg once daily for 4 weeks, which could be escalated to 8 mg once daily for the next 4 weeks based on patient's tolerability and efficacy responses. The study included 10 idiopathic and 11 neurogenic patients. Patients with NDO did not appear to have any remarkable differences in 5-HMT pharmacokinetics (PK) when compared with patients with idiopathic OAB. Clearance of 5-HMT appears to be similar in pediatric patients compared to adults when allometrically scaled by patient weight. Administration of fesoterodine 4 and 8 mg once-daily doses to pediatric patients of ages 8-17 yrs and body weight >25 kg provided steady-state plasma 5-HMT exposures similar to those in adults. There were no discontinuations due to AEs or deaths in this study; there was one serious adverse event (AE) of constipation while taking fesoterodine 8 mg, resulting in hospitalization and temporary discontinuation of study treatment. Based on the safety results, fesoterodine treatment was well tolerated by pediatric patients in Study A0221066 and there were no significant safety issues. The 3-day bladder diaries were deemed feasible and useful for assessing the OAB symptoms in both idiopathic and neurogenic pediatric patients.

**Study Rationale**

The primary purpose of this study is to evaluate the safety and efficacy of fesoterodine 4 mg and 8 mg once daily in pediatric NDO subjects aged between 6-17 years and with a body weight >25 kg, and fesoterodine 2 mg and 4 mg in subjects ≤25 kg. Additionally, the safety and efficacy of oxybutynin extended release (XL) will be evaluated in subjects >25 kg only. Sparse PK samples will also be obtained to determine the steady-state population pharmacokinetics of 5-HMT following fesoterodine treatment in pediatric NDO subjects.

The study will enroll two weight cohorts as follows:

- *Cohort 1*

  For subjects >25 kg, following 12 weeks of treatment with either fesoterodine 4 mg, 8 mg or oxybutynin XL in an active comparator phase, subjects will then enter a safety extension phase receiving either 4 mg or 8 mg of fesoterodine for an additional 12 weeks. This cohort will include subjects 25.1 kg and above.

- *Cohort 2*

  For subjects ≤25 kg, following 12 weeks of treatment with either dose of fesoterodine (2 mg, 4 mg as a beads-in-capsule formulation) in an efficacy phase, subjects will then enter a safety extension phase receiving the same doses of fesoterodine for an additional 12 weeks. This cohort will include subjects 25.0 kg and below.

In the event that it is not possible to develop an age-appropriate formulation, then lighter subjects will not be dosed, and the end of the trial will be defined by the completion of the heavier >25 Kg cohort.

**Dose Selection Rationale**

**Fesoterodine**

*Cohort 1 (Subjects >25 kg)*

Pharmacokinetic (PK) simulations were conducted based on the adult 5-HMT population PK parameters and allometric scaling of the adult population parameters applied to a distribution of pediatric patients 6-17 years of age and body weights >25 kg. The modeling and simulations (M&S) results along with the population PK results from the Phase 2 study A0221066 were used to confirm the pediatric doses for Study A0221047.

These M&S analyses predicted that following administration of fesoterodine 4 and 8 mg once-daily doses to children aged 6-17 years and weighing >25 kg body weight, the plasma 5-HMT exposures would be to be similar to those in adults given the same doses. The actual observed 5-HMT plasma concentrations from Study A0221066 are in agreement with the simulation results, and administration of fesoterodine 4 and 8 mg once-daily to pediatric patients was well tolerated and provides steady-state plasma 5-HMT exposures similar to those in adults.

Based on the PK results of Study A0221066, combined with modeling and simulations, fesoterodine 4 and 8 mg once-daily are selected as doses for this safety and efficacy Study A0221047 in NDO patients of ages 6-17 years and body weight >25 kg. If subjects cannot tolerate the dose they are randomized to they should be withdrawn from the trial as a dose reduction is not permitted in this trial.

*Cohort 2 (Subjects ≤25 kg)*

Selection of doses is based on simulations and integrated observed data from 21 children aged 6 to 17 years and >25 kg in the prior fesoterodine Study A0221066, and 19 completed subjects in the currently on-going Study A0221047, as well as the PK and bioavailability of 5-HMT following administration of the beads in the capsule formulation in adults (Study A0221068, A0221069). Modelling and simulations have been used to confirm the selection of doses in subjects ≤25 kg, with the aim of achieving 5-HMT exposures similar to those identified as safe and efficacious in subjects >25 kg and not exceeding the exposures in adults given 4 mg and 8 mg doses of fesoterodine.

The daily dose of fesoterodine in this study is 2 mg or 4 mg given once daily for subjects ≤25 kg. If subjects cannot tolerate the dose they are randomized to they should be withdrawn from the trial.

For both cohorts, the dose assigned at randomization (Day 1) will not be changed irrespective of any change in weight.

**Oxybutynin**

Subjects randomized to oxybutynin (only Cohort 1: subjects >25 kg) will receive oxybutynin extended release (XL) tablets at a starting dose in accordance with approved pediatric labeling, and accepted practice eg, oxybutynin XL 5 mg once a day. Dose optimization will be achieved by either up or down -titration in 5 mg increments on a weekly basis to achieve a balance of efficacy and tolerability. The maximum dose used in this study will not exceed the recommended dose consistent with approved pediatric labeling, and accepted practice. Subjects who took oxybutynin XL prior to study entry and who are randomized to the oxybutynin treatment group may restart on their pre-study dose. All subjects should achieve a minimum total daily dose of oxybutynin XL 10 mg by the end of the dose adjustment period at Week 4. Subjects who are unable to tolerate a minimum total dose of oxybutynin XL 10 mg once daily should be withdrawn. Dose adjustments after Week 4 are not permitted.

**Single Reference Safety Document**

Complete information for fesoterodine may be found in the Single Reference Safety Document, which for this study is the current Investigator Brochure. The Single Reference Safety Document for oxybutynin XL is the product label.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

#### 2.1.1. Primary Objectives

- To determine the safety and efficacy of fesoterodine 4 mg and 8 mg following once daily treatment for 12 weeks in pediatric NDO subjects with weight >25 kg.

- To determine the safety and efficacy of fesoterodine 2 mg and 4 mg following once daily treatment for 12 weeks in pediatric NDO subjects with weight ≤25 kg.

#### 2.1.2. Secondary Objectives

The secondary objectives of this study are to:

- evaluate the safety and efficacy of fesoterodine versus oxybutynin in pediatric NDO subjects with weight >25 kg.

- evaluate the safety of fesoterodine 4 mg and 8 mg once daily treatment for up to 24 weeks in pediatric NDO subjects with weight >25 kg.

- evaluate the safety of fesoterodine 2 mg and 4 mg once daily treatment for up to 24 weeks in pediatric NDO subjects with weight ≤25 kg.

- determine the steady-state population pharmacokinetics of 5-HMT following fesoterodine 4 mg and 8 mg once daily treatment in pediatric NDO subjects with weight >25 kg.

- determine the steady-state population pharmacokinetics of 5-HMT following treatment with two doses of fesoterodine 2 mg and 4 mg once daily in pediatric NDO subjects.

## 2.2. Endpoints

### 2.2.1. Primary Endpoint

- Maximum cystometric bladder capacity defined as maximal tolerable cystometric capacity or until voiding/leaking begins or at 40 cm $H_2O$.

### 2.2.2. Secondary Endpoints

#### 2.2.2.1. Efficacy Endpoints

- Detrusor pressure at maximum bladder capacity.

- Presence of involuntary detrusor contractions (IDC).

- Bladder volume at first IDC.

- Bladder compliance.

- Mean number of micturitions and/or catheterizations/24 hrs.

- Mean number of incontinence episodes/24 hrs.

- Mean urgency episodes/24 hrs if applicable (only for sensate subjects).

- Mean volume voided per micturition or mean volume per catheterization.

#### 2.2.2.2. Safety Endpoints

- Adverse events, including monitoring of targeted events including, but not limited to:

    - Anticholinergic effects such as dry mouth, dry eyes and constipation.

    - CNS effects such as behavioral changes (eg, aggression), decreased cognitive function, headache, seizures, somnolence.

  - Visual effects such as accommodation disorder, blurred vision, and amblyopia.

- Visual acuity and accommodation tests.

- Cognitive function by the Child Behavior Check List and Grooved Pegboard Test.

- Vital Signs, including heart rate in the context of age-appropriate norms.

- Urinary Tract Infection, as evidenced by urinalysis, urine microscopy, culture and sensitivity.

- Clinical Laboratory Evaluations in the context of age-appropriate norms, with particular reference to liver function tests and renal chemistry.

- Post-void residual volume (PVR) in subjects not performing CIC, or with >1 urinary tract infection (UTI) during the study.

#### 2.2.2.3. Pharmacokinetic Endpoints

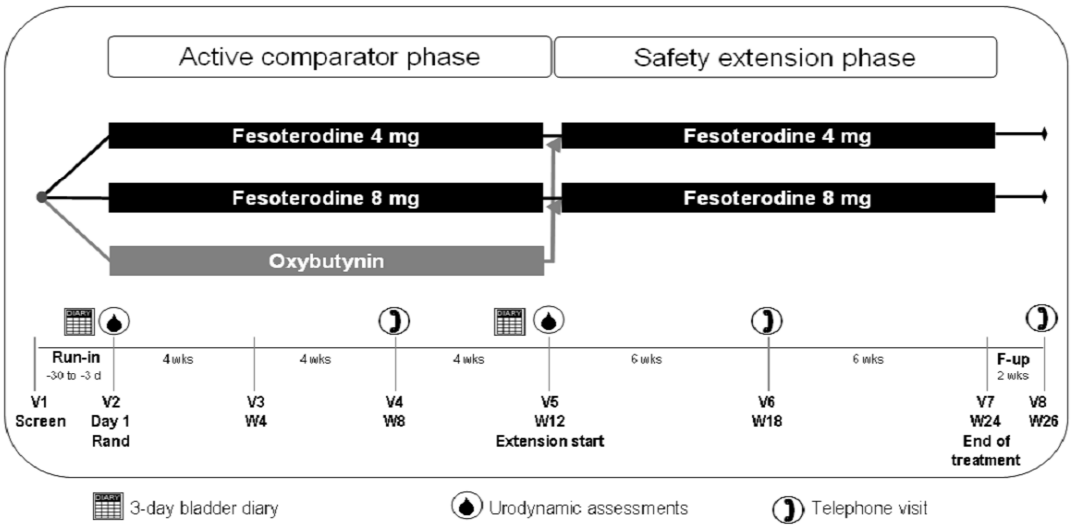
- Model-based pharmacokinetic parameter estimates for absorption rate constant (Ka), apparent oral clearance (CL/F) and volumes of distribution (Vd) to predict the area under the curve (AUC), maximum concentration ($C_{max}$), time to reach $C_{max}$ ($T_{max}$) and half-life of 5-HMT.

## 3. STUDY DESIGN

The study was designed to be in line with clinical practice and to minimize disruption, discomfort and inconvenience for subjects whilst maintaining scientific integrity.

*Cohort 1 (Subjects >25 kg)*

For this cohort this is a randomized, open label, active comparator parallel group study with three treatment arms.




Note: The first week of the fesoterodine 8 mg group will be at a dose of 4 mg each day, for the active comparator phase and for those subjects changing from oxybutynin to the safety extension phase.

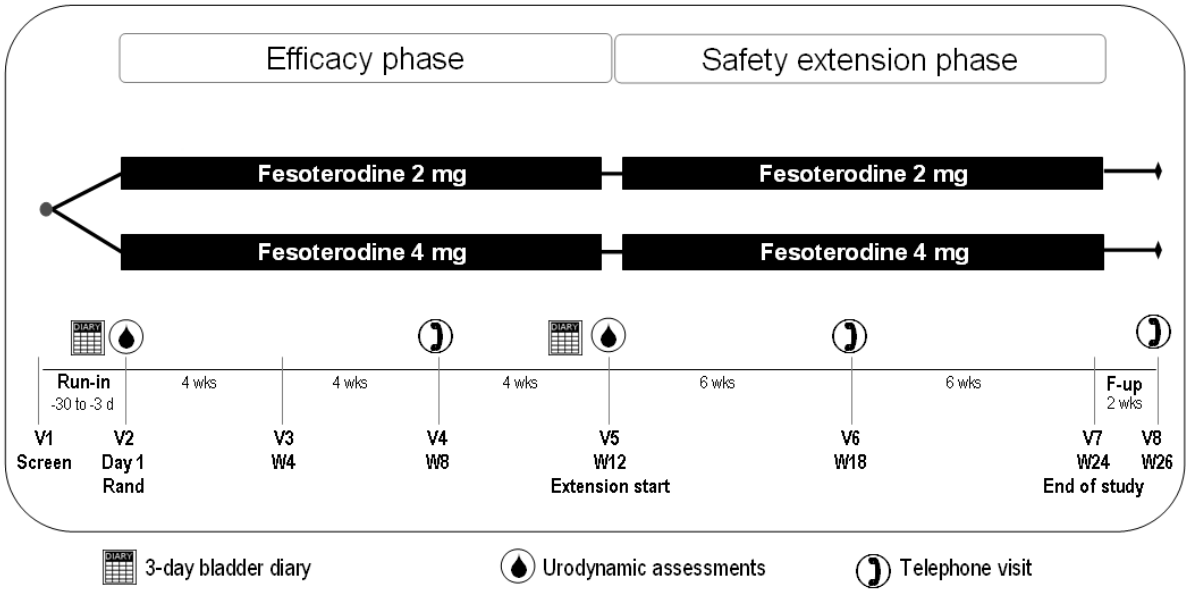
The study consists of two parts: a 12 week three arm phase with an active comparator (oxybutynin XL), followed by a 12 week two arm extension phase without the active comparator.

There is a variable screening period (minimum 3 days) prior to the baseline visit, the duration of which is principally determined by the prior medication subjects may need to washout (Appendix 3). At baseline, subjects will be randomized to one of three arms: 4 mg or 8 mg/day of fesoterodine or oxybutynin XL. Subjects will be randomized to each arm in a 1:1:1 ratio.

After 12 weeks (or earlier if appropriate), subjects in the oxybutynin arm of the study will be allocated by the investigator to fesoterodine at either 4 mg or 8 mg/day.

A sufficient number of subjects will be randomized into Cohort 1 to ensure a total of approximately 99 subjects (approximately 33 evaluable subjects per arm) are evaluable for the primary efficacy and safety analyses at Week 12, after which screening to Cohort 1 will be closed.

*Cohort 2 (Subjects ≤25 kg)*




Note: The first week of the fesoterodine 4 mg group will be at a dose of 2 mg each day, for the efficacy phase.

For this cohort the study consists of two parts: a 12 week two arm efficacy phase, followed by a 12 week two arm safety extension phase.

There is a variable screening period (minimum 3 days) prior to the baseline visit, the duration of which is principally determined by the prior medication subjects may need to washout (Appendix 3).

At baseline, subjects will be randomized to one of two fesoterodine treatment arms: doses 2 mg and 4 mg/day). Subjects will be randomized to each arm in a 1:1 ratio. Once allocated subjects will remain on that dose for the 12 week efficacy phase, and will continue at the same dose during the 12 week safety extension phase.

It is planned that a sufficient number of subjects will be randomized into this cohort to ensure a total of approximately 50 subjects (approximately 25 evaluable subjects per arm) are evaluable for the primary efficacy and safety analyses at Week 12, after which screening to Cohort 2 will be closed.

The dosing of lighter subjects is dependent on the availability of an age-appropriate Beads-in-Capsule formulation. In the event that it is not possible to develop an age-appropriate formulation, then lighter subjects will not be dosed, and the end of the trial will be defined by the completion of the heavier >25 Kg cohort.

### 3.1. Study Visits

Following Screening (V1), there are 4 additional clinic visits:

- Randomization (Day 1, V2),
- Week 4 (V3),
- Week 12 (V5) and
- Week 24 (V7).

There will also be a minimum of 3 telephone calls (or clinic visits) to subjects to identify any new adverse events, review concomitant medication usage and the dosing log at:

- Week 1
- Week 8 (V4),
- Week 18 (V6)

and a further telephone call (or clinic visit) at:

- Week 26 (V8). To review ongoing or new adverse events, review concomitant medications for subjects 2 weeks after completing study treatment. It will also be completed for all subjects who withdraw early from the study and take at least 1 dose of study medication.

In addition, subjects >25 kg randomized to treatment with oxybutynin XL may receive a minimum of 3 contacts at approximately weekly intervals between V2 and V3 for dose adjustment to achieve a balance of efficacy and tolerability up to the maximum recommended dose. The contacts may be telephone calls or clinic visits as deemed appropriate by the investigator.

Other contacts (for example, telephone calls or unscheduled clinic visits) may also be made, as appropriate, to verify study medication dose, and to provide reminders to the subject to complete the bladder diary and, if needed, daily dosing log.

After the end of the trial, continued access to fesoterodine may be provided, if it is demonstrated that fesoterodine may provide a therapeutic benefit that cannot be obtained from available marketed treatments, and it is appropriate, feasible, and allowed according to SOPs and local regulations. In this case, fesoterodine will be provided until commercially available or 30 June 2017 or until subject discontinues such continued access treatment, whichever is earlier.

## 4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

## 4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male or female subjects aged 6-17 years 11 months (age at time of first dose); that is subjects who have passed their sixth birthday but not reached their eighteenth birthday.

2. Subjects with stable neurological disease and clinically- or urodynamically-demonstrated NDO, confirmed urodynamically at Visit 2, by detrusor overactivity or decreased bladder compliance, with decreased maximum cystometric bladder capacity.

   NOTE: Subjects with hypocontractile bladder, detrusor underactivity, or a 'flaccid' bladder should not be included.

3. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study. In addition, an assent from the subject will be obtained when appropriate, and when the potential subject is capable of providing assent.

4. Female subjects who are of child-bearing potential (defined as ≥9 years old or have experienced menarche, whichever is earlier) must not be intending to become pregnant, currently pregnant, or lactating. The following conditions apply:

   a. Subjects of childbearing potential must have a confirmed negative pregnancy test prior to randomization.

   b. Subjects of child-bearing potential must agree to use effective contraception during the period of the trial and for at least 28 days after completion of treatment. Effective contraception includes abstinence.

   c. Sexually active male subjects must agree to use effective contraception during the period of the trial and for at least 28 days after completion of treatment.

   Further details of the definition of child-bearing potential and effective contraception may be found in Section 4.4.

5. Swallowing:

   a. Subjects >25 kg must already have the ability to swallow tablets whole, without chewing or crushing. The first dose of medication will be given in clinic under observation, and any subject not able to swallow tablets will be excluded from the study.

b. Subjects ≤25 kg can either swallow the capsules whole or sprinkle on food.

6. Subjects and their caregivers/parents who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

### 4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

In France, see Appendix 5.

1. Any condition known to affect drug absorption (eg, gastrectomy).

2. History of surgical procedures that could confound study results or increase the risk to subjects, including but not limited to: sphincterotomy, artificial sphincter, implantable stent, bladder augmentation procedures, urinary diversion procedures. Continent diversion procedures eg, Mitrofanoff are permitted.

3. A history of indwelling urinary catheter within 4 weeks of participation in this study. Intermittent catheterization is permitted.

4. Any comorbid condition that, in the opinion of the investigator, would confound study results or increase the risk to subjects eg, current history of bladder calculus.

5. A history of autonomic dysreflexia eg, increased blood pressure with bladder filling or other stimuli.

6. Subjects with clinically relevant out-of-range values for hematology or serum chemistry as confirmed by blood tests performed at Visit 1, and which require the subject's exclusion in the opinion of the investigator.

7. A 12-lead ECG at screening with clinically significant abnormality.

8. Unwilling or unable to comply with the Lifestyle guidelines described in this protocol.

9. Subjects required to take or expected to initiate concomitant medications that can interact with the pharmacokinetics and/or pharmacodynamics of fesoterodine or oxybutynin, such as:

   - Potent CYP3A4 inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the trial (Appendix 1).

   - Medications capable of inducing CYP3A4 enzyme metabolism (Appendix 1).

   - Drugs for the treatment of overactive bladder (eg, darifenacin, oxybutynin (including intravesical), propiverine, tolterodine, fesoterodine, solifenacin and trospium).

   - Treatment with botulinum toxin A within 9 months prior to Visit 2 (baseline).

- Drugs with antispasmodic, parasympathetic, or cholinergic effects. Stable use of desmopressin for enuresis is allowed if established for at least 3 months.

Previous treatment with these medications does not exclude subjects. However, prohibited concomitant medications must have a minimum washout appropriate to the drug so any clinical effect is at a minimum prior to beginning the bladder diary, and baseline urodynamic evaluations (Section 5.6).

10. Intermittent or unstable use of diuretics or alpha blockers, tricyclic antidepressants or any other treatment that may confound the results of the study, within 2 weeks or an appropriate washout period (whichever is longer) prior to starting the bladder diary or during the course of the study. Stable usage/dosage is allowed if established for at least 3 months.

11. Electrostimulation therapy or bladder retraining if started within 30 days of Visit 1 or are expected to start such therapy during the study period. Subjects who are on an established regimen may remain on this for the duration of the study.

12. Subjects with a clinically significant urinary tract infection (UTI) at screening.

    Urine microscopy, culture and sensitivity testing will be performed in the event of:

    - presence of symptoms (eg, fever, flank pain), or
    - positive leucocytes and/or nitrites on urinalysis, or
    - if subject has a documented history of vesicoureteral reflux (VUR).

    A clinically significant UTI is defined as:

    - positive urine culture with a uropathogen (defined as $\geq 10^5$ CFU/ml) and the presence of symptoms, or
    - pyuria (defined as >50 white blood cells (WBC)/hpf) and the presence of symptoms, or
    - positive urine culture with a uropathogen (defined as $\geq 10^5$ CFU/ml) with or without symptoms in a subject with a documented history of VUR.

      Subjects who are found to have an active UTI during screening may continue screening activities on resolution of symptoms or treatment of the UTI to the satisfaction of the treating physician.

13. Subjects not requiring intermittent catheterization who have a post-void residual volume greater than 20 ml as determined by transabdominal ultrasound (eg, bladder scan) immediately after urination. If at screening, the PVR is found to be greater than 20 ml the subject will be asked to void again. Repeat PVR assessment should be made as soon

as possible, and no more than 5 minutes, after the second void. Subjects found to have a persistently elevated PVR >20 ml at this visit will be excluded from the study.

14. Subjects with any history of malignancy.

15. Subjects with any condition or at risk of any condition that would contraindicate or warrant precautions for the use of fesoterodine or oxybutynin, including:

    - Hypersensitivity to fesoterodine, tolterodine or oxybutynin.
    - Known history of hypersensitivity to peanut or soya or any of the excipients of the fesoterodine or oxybutynin formulation.
    - Gastric retention.
    - Severely decreased gastrointestinal motility (not under active management).
    - Uncontrolled narrow angle glaucoma.
    - Gastrointestinal obstructive disorders.
    - Myasthenia gravis.
    - Severe hepatic impairment (Child Pugh C).
    - Severe ulcerative colitis.
    - Toxic megacolon.

16. Previously received any investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to Visit 1. Participation in other studies within 4 weeks before the current study begins or during study participation.

17. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

18. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

### 4.3. Continuation Criteria

There must be no urodynamic evidence of clinically relevant increased detrusor pressure or other urodynamic findings suggestive of worsening condition compared to baseline, prior to continuation in the Safety Extension period.

### 4.4. Lifestyle Guidelines

Subjects should maintain their normal daily routine, and changes in lifestyle during the course of the study should be avoided.

Subjects should avoid the consumption of grapefruit juice as it interferes with the metabolism of fesoterodine.

Female subjects of childbearing potential

Childbearing potential is defined as female subjects ≥ 9 years old or have experienced menarche, whichever is earlier, and who are anatomically and functionally able to conceive. Subjects of childbearing potential must have a confirmed negative pregnancy test prior to randomization.

Female subjects must agree to use effective contraception during the period of the trial and for at least 28 days after completion of treatment. Male subjects must agree to use effective contraception during the period of the trial and for at least 28 days after completion of treatment.

Acceptable effective forms of contraception include:

- Abstinence;
- Barrier method, eg, condom with spermicidal foam/gel/film/cream/suppository;
- Hormonal contraceptives: (oral, injected, intrauterine, transdermal or implanted) provided the subject remains on the treatment throughout the entire study and has been using hormonal contraceptives for an adequate period of time to ensure effectiveness.

Where there is uncertainty over contraceptive requirements, or an unusual method is being used for this population (such as an intrauterine device) the Pfizer medical expert must be contacted to determine if the subject is suitable for study participation.

### 4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the study portal.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains,

at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

## 5. STUDY TREATMENTS

### 5.1. Fesoterodine

*Cohort 1 (Subjects >25 kg)*

Subjects randomized to fesoterodine will receive either 4 mg or 8 mg fesoterodine PR tablets once daily throughout the initial 12 weeks of the active comparator phase and will continue at the same dose during the 12 week safety extension phase. All those assigned to the fesoterodine 8 mg arm will start at 4 mg daily for one week, and will then escalate to 8 mg daily. If subjects cannot tolerate the dose they are randomized to they should be withdrawn from the trial as a dose reduction is not permitted in this trial.

*Cohort 2 (Subjects ≤25 kg)*

Subjects will be randomized to either 2 mg or 4 mg fesoterodine BIC capsules once daily throughout the initial 12 weeks of the efficacy phase and will continue at the same dose during the 12 week safety extension phase. All those assigned to the fesoterodine 4 mg arm will start at 2 mg daily for one week and will then escalate to 4 mg daily. If subjects cannot tolerate the doses they are randomized to, they should be withdrawn from the trial as a dose reduction is not permitted on this trial.

For both cohorts, it is expected that all subjects will also complete the extension phase unless, in the judgment of the investigator, this is not appropriate. Subjects can withdraw from the study at any time.

### 5.2. Oxybutynin (Subjects >25 kg)

Subjects in Cohort 1 (weight >25 kg) randomized to oxybutynin will receive oxybutynin extended release (XL) tablets at a starting dose in accordance with approved pediatric labeling, and accepted practice eg, oxybutynin XL 5 mg once a day. Dose optimization will be achieved by either up or down titration in 5 mg increments on an approximately weekly basis to achieve a balance of efficacy and tolerability. All subjects should achieve a minimum total daily dose of oxybutynin XL 10 mg by the end of the dose adjustment period

at Week 4. The maximum dose used in this study will not exceed the recommended dose consistent with approved pediatric labeling, and accepted practice. Subjects who were on oxybutynin prior to study entry and who are randomized to the oxybutynin XL treatment group may, at the discretion of the investigator, restart at the equivalent pre-study total daily dose.

After Week 4, subjects taking oxybutynin XL should remain on the same dose for the subsequent 8 weeks of the study, and no further dose adjustments should be permitted. Subjects who are unable to tolerate a minimum total dose of oxybutynin XL 10 mg once daily should be withdrawn. Subjects who withdraw from the oxybutynin treatment arm for reasons of toleration, and who fulfill all continuation criteria, may be directly allocated by the investigator to fesoterodine treatment at either 4 mg or 8 mg/day for the remaining 12 week safety extension period. All those assigned to the fesoterodine 8 mg arm will start at 4 mg daily for one week, and will then escalate to 8 mg daily. All subsequent study visits should be scheduled relative to the start of the extension phase.

At Visit 5 (or earlier if appropriate), subjects in the oxybutynin arm of the study will be allocated by the investigator to fesoterodine at either 4 mg or 8 mg/day. Subjects should undergo a minimum 2 day washout period from oxybutynin prior to starting treatment with Fesoterodine. All those assigned to the fesoterodine 8 mg arm will start at 4 mg daily for one week, and will then escalate to 8 mg daily. Once allocated the dose will remain fixed for the period of the extension; if treatment is inadequate or the subject cannot tolerate the dose, consideration should be given to withdrawal.

### 5.3. Allocation to Treatment

This is an open label study. The study will use an automated telerandomization system incorporating a central randomization scheme; however separate randomization schedules will be maintained for Cohort 1 and Cohort 2. At Visit 2, randomization, subjects will be randomly assigned to their treatment group according to a computer generated pseudorandom code using the method of random permuted blocks. At Visit 5, start of extension period, subjects in the oxybutynin group in Cohort 1 (>25 kg) will be allocated to fesoterodine 4 mg or 8 mg, according to the investigator's judgment.

For Cohort 1 (subjects >25 kg), in order to ensure an appropriate balance of subjects in each treatment group across the whole body weight spectrum, subjects will be stratified at randomization into two groups dependent on their body weight. The lower weight group within Cohort 1 will include all those with a weight of 50 kg or less and the higher weight group within Cohort 1 will include all those above 50 kg.

Cohort 2 (subjects ≤25 kg) will not be stratified.

As this is an open-label study, drug supply will not be blinded, however due to the central randomization and automated telerandomization system, the investigator’s knowledge of the treatment assigned to each subject should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

## 5.4. Drug Supplies

### 5.4.1. Formulation and Packaging

**Fesoterodine**

For Cohort 1 (subjects >25 kg), fesoterodine PR 4 mg and 8 mg will be provided by Pfizer as tablets. The tablets will be packaged by Pfizer according to applicable regulatory requirements. Both the 4 mg and 8 mg dosage forms are tablets designed for oral administration. The tablets should be taken orally with water without chewing. The study medication is a blue, oval tablet. The subject will take one tablet daily as a single dose.

At Visit 2, subjects will be provided study medication for 4 weeks. At Visit 3, subjects will be provided study medication for 8 weeks. At Visit 5 (beginning of the safety extension phase), subjects will be provided study medication for 12 weeks.

For Cohort 2 (subjects ≤25 kg), subjects will be randomized to one of the two arms of the study, fesoterodine 2 mg or 4 mg once daily per the randomization schedule for this cohort. Fesoterodine 2 mg and 4 mg once daily will be provided by Pfizer as a beads-in-capsule (BIC) formulation. The BIC will be packaged by Pfizer according to applicable regulatory requirements. Both dosage forms are capsules designed for oral administration. The capsules should be taken orally with water without chewing. For subjects who cannot swallow whole capsules, the capsule may be opened and the beads sprinkled on a suitable medium (eg, apple sauce) as directed by the Investigator or approved representative (eg, pharmacist).

At Visit 2, the subjects will be provided study medication for 4 weeks. At Visit 3, subjects will be provided study medication for 8 weeks. At Visit 5 (beginning of the Safety Extension Phase), subjects will be provided study medication for 12 weeks. The subject will take one capsule daily as a single dose.

Subjects >25 kg (Cohort 1) who cannot swallow tablets are not permitted to take the BIC formulation and are excluded from the study.

**Oxybutynin (Subjects >25 kg)**

Commercially available oxybutynin XL 5 mg and 10 mg tablets will be sourced by Pfizer, labeled in accordance with applicable regulatory requirements, and provided to the trial sites. Both the 5 mg and 10 mg dosage forms are tablets designed for oral administration. Subjects will take oxybutynin in accordance with manufacturer and investigator or an approved representative (eg, pharmacist) instruction. In exceptional circumstances and for countries where oxybutynin XL is locally approved, supplies may be obtained by the investigator or an approved representative (eg, pharmacist) to cover for unforeseen interruptions in the Pfizer central supply. The tablets will be provided to subjects by the trial site according to applicable regulatory requirements.

Oxybutynin will only be dosed during the active comparator phase (Cohort 1), and will be used according to approved pediatric labeling and accepted practice. At Visit 2, the subjects will be provided study medication for 4 weeks according to investigator judgment. At Visit 3, subjects will be provided study medication for 8 weeks according to investigator judgment.

### 5.4.2. Preparation and Dispensing

Pfizer will provide sufficient amounts of the fesoterodine and oxybutynin XL study medications to the investigator.

The investigator, or an approved representative (eg, pharmacist) must ensure that deliveries of investigational product from the Sponsor are correctly received by a responsible person (eg, pharmacist), that all receipts are recorded in writing and that the products are stored in a secure area under recommended storage conditions. It is also the responsibility of the investigator or designated personnel to ensure that the integrity of the packaged study product not be jeopardized prior to dispensing. Each individual subject container must be dispensed as provided by Pfizer with no further repackaging or labeling done at the trial site.

Oxybutynin XL (subjects > 25 kg) will only be dispensed at one dosage strength (eg 5 mg) to avoid mis-dosing errors during the titration phase of the study. If a subject is up-titrated to a dose level where the 10 mg tablet would be more convenient, then they must visit the site to return their 5 mg tablet supply and be dispensed 10 mg tablets. When a subject has previously taken Oxybutynin XL where an established combination of dosage strengths have been used, they may continue with this regimen and be dispensed the appropriate combination. The investigator or an approved representative (eg, pharmacist) will dispense the study medications in accordance with this protocol, and applicable regulatory requirements and regulations. The investigator or approved representative (eg, pharmacist) will administer/dispense the study medication only to subjects included in this study following the procedures set out in the study protocol. The investigator or an approved representative (eg, pharmacist) is responsible for assuring retrieval of all study supplies from the subjects.

The investigator or approved representative (eg, pharmacist) must maintain accurate and adequate records including date of receipt and return of drug shipments, lot number and quantities received/returned from/to Pfizer or CRO designee, and dates and amounts dispensed to and returned by the study subjects. All full, partial full and empty drug containers must be returned to Pfizer or the CRO designee for drug accountability.

### 5.4.3. Administration

Study drug will be prepared in an open-label fashion.

*Cohort 1 (subjects >25 kg)*

Subjects will be instructed to take study medication according to this protocol. Subjects must take their first dose of study medication in clinic, to ensure correct dosing and tablet swallowing ability.

For fesoterodine 4 mg and 8 mg, subjects will swallow one tablet each day without chewing. For oxybutynin XL, subjects will take the medication as directed by the investigator or an approved representative (eg, pharmacist) per the dosing instructions described in Section 5.2.

*Cohort 2 (subjects ≤25 kg)*

Subjects will be instructed to take study medication according to instructions which will be supplied separately. Subjects will take one capsule per day without chewing. For subjects who cannot swallow whole capsules, the capsule may be opened and the beads sprinkled on a suitable medium (eg, apple sauce). Subjects must take their first dose of study medication in clinic, to ensure correct dosing.

*Both cohorts*

Subjects will also be asked to complete a daily dosing log (Section 7.5). If information from the dosing log indicates that the subject has not taken study drug in accordance with dosing instructions, the subject and their legal representative(s) will be re-instructed on how to take the study medication, and followed-up as appropriate by the investigator or approved representative to ensure understanding and compliance.

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRFs and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to Adverse Event Reporting (Section 8) for further details).

### 5.4.4. Compliance

If the tablet/capsule count from the returned study medication, or information from the daily dosing log, indicates the subject has not taken all prescribed study drug, the subject and their

legally acceptable representative(s) will be counseled about the importance of compliance and how to take the study medication.

Compliance with the study medication will be calculated for each subject using the following formula:

$$\frac{\textit{Total number of tablets/capsules used}}{\textit{Total number of tablets}/\text{capsules}\ \textit{supposed to be taken in each treatment period}} \times 100$$

It is assumed that a subject takes or returns all of the study medication provided. The denominator will be either the total number of tablets/capsules supposed to be taken prior to discontinuation or the total number of tablets/capsules supposed to be taken until the end of the study period for early termination and completed subjects, respectively.

Subject compliance for study medication should meet at least 80% of ideal compliance at the end of each study period (Week 12 and Week 24, or early termination). If the subject's compliance is below this for any study period, this will be recorded as a protocol deviation. If the subject's compliance is greater than 120%, then they should be counseled on proper dosing of study medication, and recorded as a protocol deviation. In either case, subjects with evidence of continued poor study compliance should be withdrawn. Additionally, compliance with dosing will be assessed for at least 3 days prior to PK sampling at Visit 3 and one day prior to urodynamic evaluation at Visit 5.

### 5.5. Drug Storage and Drug Accountability

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a securely locked area accessible only to authorized personnel, under recommended storage conditions, and in accordance with applicable regulatory requirements and the manufacturer's instructions. Study drug supplies must be stored separately from normal hospital/practice stocks. Fesoterodine PR 4 mg and 8 mg tablets and oxybutynin XL should be stored according to the product label. The storage conditions stated in the Investigator Brochure may be superseded by the storage conditions indicated on the label. It is the responsibility of the investigator/site to properly store and monitor drug supplies and to report any deviations immediately.

The BIC product (2 and 4 mg) should be stored at 2°-8°C (36°- 46°F). Fesoterodine PR tablets should be stored at room temperature (15°- 25°C, [59°- 77°F]).

The investigator or an approved representative (eg, pharmacist) must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational product(s). Pfizer may supply drug accountability forms that must be used or may approve the use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a

subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.

At Visits 3, 5 and 7, subjects must return all unused study medication and packaging (eg, bottles) to the investigator or an approved representative (eg, pharmacist). This includes all study medications (fesoterodine and oxybutynin) and packaging (eg, bottles), whether provided by Pfizer or obtained commercially.

At the end of the trial, Pfizer will provide instructions as to disposition of any unused investigational product, including packaging (eg, bottles). If Pfizer authorizes destruction at the trial site, the investigator or an approved representative (eg, pharmacist) must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

If oxybutynin XL (subjects >25 kg) is locally sourced (in exceptional circumstances, see Section 5.4.1), it should be sourced, stored and disposed of in accordance with label instructions and applicable regulatory requirements and regulations.

### 5.6. Concomitant Medication(s)

Prior and concomitant medication information will be collected for all subjects for a period of 30 days prior to screening and during the study. Information collected must include medication, total daily dose, start date, stop date (if applicable), and primary reason for use.

#### 5.6.1. Permitted Concomitant Therapies

The following concomitant therapies are permitted:

- Stable usage/dosage of diuretics, alpha blockers, or tricyclic antidepressants is allowed if established for at least 3 months.
- Stable use of desmopressin for enuresis is allowed if established for at least 3 months.
- Subjects who are on an established regimen of electrostimulation therapy or bladder retraining (for at least 30 days prior to Visit 1) may remain on this for the duration of the study.

#### 5.6.2. Prohibited Concomitant Therapies

The following concomitant therapies are not permitted:

- Potent CYP3A4 inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the trial (Appendix 1).
- Medications capable of inducing CYP3A4 enzyme metabolism (Appendix 1).

- Drugs for treatment of overactive bladder, (eg, darifenacin, oxybutynin (including intravesical), propiverine, tolterodine, fesoterodine, solifenacin and trospium).

- Treatment with botulinum toxin A within 9 months prior to Visit 2 (baseline).

- Drugs with antispasmodic, parasympathetic, or cholinergic effects.

- Intermittent or unstable use of diuretics or alpha blockers, tricyclic antidepressants or any other treatment that may confound the results of the study, within 2 weeks or an appropriate washout period (whichever is longer) prior to starting the bladder diary or during the course of the study.

- Electrostimulation therapy or bladder retraining if started within 30 days of Visit 1 or started during the study period. Subjects who are on an established regimen may remain on this for the duration of the study.

- Treatment with an investigational drug within 4 weeks or 5 half-lives (whichever is the longer) preceding study entry.

Previous treatment with these medications does not exclude subjects. However, prohibited concomitant medications must have a minimum washout appropriate to the drug so any clinical effect is at a minimum prior to beginning the bladder diary, and baseline urodynamic evaluations eg, 3 day minimum washout for oxybutynin, 7 day minimum washout for darifenacin and solifenacin. (Appendix 3).

Subjects should avoid the consumption of grapefruit juice as it interferes with the metabolism of fesoterodine.

The agreement of the subject and their legally-acceptable representative(s) should be gained before withdrawal of any therapies.

## 6. STUDY PROCEDURES

### 6.1. Visit 1 (Screening, Day -30 to Day -3)

The screening visit may be conducted over separate days, if required. The following assessments will be performed:

- Informed consent and subject assent prior to any screening assessments.

- Obtain subject demographic details.

- Evaluation of subject's eligibility based on inclusion and exclusion criteria.

- Perform medical history, including whether the subject is sensate (ie, physically able to experience the sensation of urgency).

- Perform concomitant medication review.
- Perform electrocardiogram.
- Measure vital signs (blood pressure, heart rate, temperature) after the subject has been in a sitting/resting position for at least 5 minutes.
- Perform physical examination and weight measurement. Note that weight determines formulation assignment at the Randomization Visit 2.
- In subjects who are not performing intermittent catheterization, perform post-void residual (PVR) urine volume assessment using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. PVR assessment is not required in subjects who empty their bladder using intermittent catheterization unless otherwise indicated (Section 7.2.6).
- Clinical laboratory testing (approximately 5.5 ml of blood; see Appendix 2) including:
  - Hematology.
  - Blood chemistry.
  - Serum pregnancy test for all female subjects of childbearing potential.
  - Urinalysis and urine microscopy, culture and sensitivity if indicated.
- Dispense electronic data capture device and instruction booklet.
- Train subject and their caregiver on use of bladder diary in the electronic data capture device.

Subjects who are found to have an active UTI during screening may continue screening activities on resolution of symptoms or treatment of the UTI to the satisfaction of the treating physician. Screening assessments which have already been performed do not need to be repeated, unless otherwise indicated, or if they will be >30 days before Day 1 (Randomization).

### 6.2. Visit 2 (Randomization/Baseline, Day 1)

The following assessments will be performed at the Randomization visit which can be over separate days:

- Evaluation of subject's eligibility based on inclusion and exclusion criteria.
- Perform concomitant medication review.
- Perform review of adverse events occurring after signing the informed consent document.

- Complete Child Behavior Checklist (CBCL).
- Complete Grooved Pegboard Test.
- Review bladder diary for completeness and check subject understanding of completion.
- Measure vital signs (blood pressure, heart rate, temperature) after the subject has been in a sitting/resting position for at least 5 minutes.
- In subjects who are not performing intermittent catheterization, perform post-void residual (PVR) urine volume assessment using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. PVR assessment is not required in subjects who empty their bladder using intermittent catheterization unless otherwise indicated (Section 7.2.6).
- Visual acuity and accommodation assessment.
- Urine pregnancy test for all female subjects of childbearing potential.
- Perform urodynamic assessment.
- Train subject and their caregiver on use of electronic dosing log and check they still have the instruction booklet dispensed at Visit 1.
- Dispense appointment & dosing record card (for oxybutynin subjects only).
- Dispense study medication, administer and observe first dose.

The electronic data capture device should be collected at this visit if the subject is not subsequently randomized.

### 6.3. Week 1 Telephone Call (±2 days)

The following assessments will be performed at Week 1 by telephone or clinic visit:

- Concomitant medication review.
- Review of adverse events.
- Review dosing log and remind subjects randomized to fesoterodine 8 mg(Cohort 1), that they will need to change from the 4 mg dose to the 8 mg dose, and those randomized to fesoterodine 4 mg (in Cohort 2), that they will need to change from the 2 mg dose to the 4 mg dose.
- Dose optimization review for oxybutynin group subjects (see Section 6.4, not applicable to Cohort 2).

### 6.4. Dose Optimization of Oxybutynin (Weeks 1, 2 and 3, ±2 days) (Subjects >25 kg)

Subjects randomized to oxybutynin will have their dose adjusted at weekly intervals during the first 4 weeks of the study. Only oxybutynin tablets of one dosage strength will be dispensed at Visit 2. There should be a minimum of 3 contacts between V2 and V3 to assess efficacy and tolerability. The contacts with the subject's parent/guardian (caregiver) may be by telephone calls or clinic visits as considered clinically appropriate following assessment by the investigator. The investigator will record dose adjustments in the medical records and CRF, and the caregiver will keep a telephone appointment and dosing log, to record the instructions they have been given. In addition, within a few days of any change in oxybutynin dose, there should be verification that caregivers have correctly understood the change in the subject's dose regimen eg, by telephone contact, or by confirmation of dosing information captured in the subject's dosing log.

Subjects randomized to oxybutynin will receive oxybutynin extended release (XL) tablets at a starting dose in accordance with approved pediatric labeling, and accepted practice eg, oxybutynin XL 5 mg once a day. Dose optimization will be achieved by either up- or down-titration in 5 mg increments on an approximately weekly basis to achieve a balance of efficacy and tolerability. Subjects who were on oxybutynin prior to study entry and who are randomized to the oxybutynin XL treatment group may, at the discretion of the investigator, restart at the equivalent pre-study total daily dose.

Subject's caregivers should receive a contact approximately 1 week after starting oxybutynin to assess efficacy and tolerability, and to adjust the dose as appropriate. Healthcare professionals deciding the dose adjustments must be medically-qualified and have prescribing authority, eg, MD. Qualifications of delegates will be reviewed and agreed with the Pfizer study team as part of the standard site pre-trial assessment procedure, and prior to any subject enrollment.

Two additional contacts should be made, approximately 1 week apart, and the oxybutynin dose adjusted to optimum efficacy and tolerability up to the maximum recommended dose consistent with approved pediatric labeling, and accepted practice. All subjects should achieve a minimum total daily dose of oxybutynin XL 10 mg by the end of the dose adjustment period at Week 4. After Week 4, subjects taking oxybutynin XL should remain on the same dose for the subsequent 8 weeks of the study, and no further dose adjustments should be made. Subjects who are unable to tolerate a minimum total daily dose of oxybutynin XL 10 mg should be withdrawn.

Subjects who withdraw from the oxybutynin treatment arm for reasons of toleration, and who fulfill all continuation criteria, may be directly allocated by the investigator to fesoterodine treatment at either 4 mg or 8 (initially 4) mg/day for the remaining 12 week safety extension period if deemed appropriate during which dose reductions will not be permitted; if the fesoterodine is not tolerated then the subject will be withdrawn. All subsequent study visits should be scheduled relative to the start of the extension phase.

The following assessments will also be performed:

- Concomitant medication review;
- Review of adverse events;
- Review dosing log.

### 6.5. Visit 3 (Week 4, ±14 days)

The following assessments will be performed at Visit 3:

- Concomitant medication review;
- Review of adverse events;
- Measure weight and vital signs (blood pressure, heart rate, temperature) after the subject has been in a sitting/resting position for at least 5 minutes;
- Urinalysis and urine microscopy, culture and sensitivity if indicated;
- In subjects who are not performing intermittent catheterization, perform post-void residual (PVR) urine volume assessment using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. PVR assessment is not required in subjects who empty their bladder using intermittent catheterization unless otherwise indicated (Section 7.2.6).
- For fesoterodine arms only, pharmacokinetic blood samples taken (maximum of 3 samples, approximately 2 ml of blood per sample; (Appendix 2).
- For fesoterodine arms only, pharmacogenomic blood sample taken (one sample, approximately 2 ml of blood; (Appendix 2) if the subject does not have prior laboratory documentation of CYP2D6 genotype.
- Urine pregnancy test for all female subjects of childbearing potential.
- Review dosing log and record time of last 3 doses of fesoterodine and re-train if necessary, and review electronic capture device.
- Study medication return/count.
- Dispense study medication.

### 6.6. Visit 4 (Week 8, ±14 days)

The following assessments will be performed at Visit 4 by telephone or clinic visit:

- Concomitant medication review.
- Review of adverse events.

- Review dosing log.

### 6.7. Visit 5 (Week 12, -7 days to +14 days)

Visit 5 may be performed over 2 separate days if required. The following assessments will be performed:

- Perform concomitant medication review.
- Perform review of adverse events.
- Complete Child Behavior Checklist (CBCL).
- Complete Grooved Pegboard Test.
- Review bladder diary for completeness and check subject understanding of completion.
- Perform physical examination and weight measurement.

  Measure vital signs (blood pressure, heart rate, temperature) after the subject has been in a sitting/resting position for at least 5 minutes.
- In subjects who are not performing intermittent catheterization, perform post-void residual (PVR) urine volume assessment using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. PVR assessment is not required in subjects who empty their bladder using intermittent catheterization unless otherwise indicated (Section 7.2.6).
- Visual acuity and accommodation assessment.
- Clinical laboratory testing (approximately 5.5 ml of blood; see Appendix 2) including:
  - Hematology.
  - Blood chemistry.
  - Urine pregnancy test for all female subjects of childbearing potential.
  - Urinalysis and urine microscopy, culture and sensitivity if indicated.
- For subjects who had oxybutynin during the active comparator phase (Cohort 1, subjects >25 kg), pharmacogenomic blood sample taken (one sample, approximately 2 ml of blood; (Appendix 2) if the subject does not have prior laboratory documentation of CYP2D6 genotype and they are to continue in the safety extension).
- Perform urodynamic assessment including imaging of upper urinary tract if appropriate. Subjects who demonstrate a clinically relevant increased detrusor pressure compared to

baseline pressure or other urodynamic findings suggestive of worsening condition should not be allowed to continue into the safety extension phase.

- Review dosing log, and record details of time of last dose of fesoterodine or oxybutynin, and review electronic capture device.
- Collect appointment & dosing record card (for oxybutynin subjects only).
- Study medication return/count; assess compliance with study medication regimen.
- Dispense study medication.

### 6.8. Visit 6 (Week 18, ±14 days)

The following assessments will be performed at Visit 6 by telephone or clinic visit:

- Concomitant medication review;
- Review of adverse events;
- Review dosing log.

### 6.9. Visit 7 (Week 24, -7 days to +14 days)

The following assessments will be performed at Visit 7:

- Concomitant medication review.
- Review of adverse events.
- Complete Child Behavior Checklist (CBCL).
- Complete Grooved Pegboard Test.
- Perform physical examination and weight measurement.
- Measure vital signs (blood pressure, heart rate, temperature) after the subject has been in a sitting/resting position for at least 5 minutes.
- Visual acuity and accommodation assessment.
- Clinical laboratory testing (approximately 5.5 ml of blood; see Appendix 2) including:
  - Hematology.
  - Blood chemistry.

- Urine pregnancy test for all female subjects of childbearing potential.
- Urinalysis and urine microscopy, culture and sensitivity if indicated.

- In subjects who are not performing intermittent catheterization, perform post-void residual (PVR) urine volume assessment using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. PVR assessment is not required in subjects who empty their bladder using intermittent catheterization unless otherwise indicated (Section 7.2.6).
- Review dosing log.
- Collect electronic data capture device.
- Study medication return/count; assess compliance with study medication regimen.

### 6.10. Visit 8 (Follow-up, Week 26 +14 days)

The following assessments will be performed at Visit 8 by telephone or clinic visit:

- Concomitant medication review;
- Review of adverse events.

Subjects who withdraw early from the study and who have taken at least 1 dose of study medication should be contacted by telephone approximately 2 weeks after stopping study medication.

### 6.11. Additional Contacts

Other contacts may also be made, as appropriate, to verify changes in dose, and to provide reminders to the subject to complete the bladder diary and daily dosing log. Contacts may take the form of telephone calls. Subjects should be contacted:

- At Week 1 to verify that they have correctly understood their dose regimen and if necessary to remind the subject to complete their daily dosing log. Subjects randomized to fesoterodine 8 mg, who have started at 4 mg should be reminded to start taking the 8 mg dose. Subjects randomized to fesoterodine 4 mg in Cohort 2 (≤25 kg), who have started at 2 mg should be reminded to start taking the 4 mg dose.
- 1 week after Visit 5, to verify that subjects previously taking oxybutynin have correctly understood their dosing regimen, and a reminder for those allocated to the 8 mg dose that they need to change from the initial 4 mg to the 8 mg dose.
- Approximately 1 week prior to Visit 2 (unless the randomization visit occurs within 1 week of Screening (V1)) and prior to Visit 5, to remind the subject to complete the bladder diary and to review instructions on proper completion if needed. Subjects and/or

their caregivers should be re-educated and re-trained if review of data suggests that the bladder diary or dosing log are not being correctly completed.

### 6.12. Subject Withdrawal

In France, see Appendix 5.

If treatment is inadequate or the subject cannot tolerate the dose of fesoterodine or oxybutynin, consideration should be given to withdrawal.

Subjects who withdraw from the oxybutynin treatment arm (Cohort 1, >25 kg) for reasons of toleration, and who fulfill all continuation criteria, may be directly allocated by the investigator to fesoterodine treatment at either 4 mg or 8 mg/day for the remaining 12 week safety extension period if appropriate. All subsequent study visits should be scheduled relative to the start of the extension phase.

Subjects may withdraw from the study at any time at their own, or their legal representative(s) request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s) and electronic diary equipment, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

Subjects in the fesoterodine groups who withdraw prior to Week 4 should have PK samples obtained as per Visit 3.

If a subject withdraws from the study prior to Visit 5 (Week 12), the same assessments as at Visit 5 should be performed if possible. Urodynamic assessment should only be performed in subjects who have been on a stable dose of study medication for at least 2 weeks, and who have not missed any doses in the 3 days prior to the visit.

If a subject withdraws from the study after Visit 5, the same assessments as at Visit 7 (Week 24) should be performed if possible.

Subjects who withdraw early from the study and who have taken at least 1 dose of study medication should also be contacted by telephone approximately 2 weeks after stopping study medication, and have the same assessments performed as at Visit 8 (Week 26).

If the subject withdraws from the study, and they or their legal representative(s) also withdraw consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

# 7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make the test unfeasible to perform. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which they have taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

## 7.1. Efficacy Assessments

### 7.1.1. Urodynamic Assessments

Urodynamic assessment will be performed by persons qualified to perform pediatric urodynamics by education, training and experience, in accordance with International Children's Continence Society standards at Visit 2 (baseline) and Visit 5 (Week 12), (Neveus, et al, 2006).[3] It should be performed with the subject awake, or if necessary under sedation, but general anesthesia is not permitted under this protocol. At Visit 2, previous treatment with prohibited concomitant medications must have a minimum washout appropriate to the drug so any clinical effect is at a minimum prior to baseline urodynamic evaluations eg, 3 day minimum washout for oxybutynin, 7 day minimum washout for darifenacin and solifenacin. At Visit 5 (Week 12), the time of the last dose of study medication (fesoterodine 2 mg, fesoterodine 4 mg, fesoterodine 8 mg or oxybutynin XL) prior to the urodynamic assessment should be recorded, and when possible urodynamic assessments should be completed approximately 4-6 hours post-dose. Typically a multichannel technique through a dual-lumen urodynamic catheter should be used. The bladder will be filled at a constant fill rate with test medium warmed to body temperature, until maximum cystometric capacity is reached as defined below, or in the judgement of the investigator, filling should be stopped.

Expected bladder capacity for age (mL) = [30 + (child's age in years x 30)] mL up to the age of 12 years. From the age of 12 years onwards EBC is relatively constant at 390 ml.

The infusion rate should be based on 5% of expected bladder capacity per minute and will be recorded on the CRF.

The following will be evaluated:

- Maximum cystometric capacity, defined as maximal tolerable cystometric capacity, until voiding or leaking begins, or at a pressure of ≥40 cm $H_20$.
- Detrusor pressure at maximum bladder capacity.
- Maximum detrusor pressure.

- Presence of involuntary detrusor contractions (IDC).
- Bladder volume at first IDC, if present.
- Bladder wall compliance (ml/cm $H_2O$), defined as Δvolume/Δpressure during that change in bladder volume.
- Presence of subtraction test (eg cough) on urodynamic trace.

Where possible, both V2 and V5 urodynamic assessments for a subject should be performed by the same person. For all subjects, eligibility for study entry or continuation on the basis of urodynamic criteria will be verified by a central reader. Only the central reader's assessment of the urodynamic evaluation should be recorded in the CRF.

Prophylactic antimicrobial treatment may be administered at the discretion of the investigator and in line with local practice.

Attempts should be made to perform a urodynamic assessment in subjects who withdraw prior to Visit 5 (Week 12) and after a minimum of 2 weeks on a stable dose of study medication, provided that they have not missed any doses in the three days prior to the visit.

At Visit 5 (or end of active comparator/efficacy phase), subjects who demonstrate a clinically relevant increased detrusor pressure, or other urodynamic findings suggestive of worsening condition compared to baseline, should not be allowed to continue into the safety extension phase. In this case, consideration should be given to imaging of upper urinary tract (for example, videourodynamics or ultrasound) according to accepted local standard of care in subjects with VUR, or other conditions that predispose to upper urinary tract dysfunction or damage.

Full technical details are provided separately.

### 7.1.2. Bladder Diary

A bladder diary will be completed for 3 consecutive days (with a minimum of 2 days) during the week prior to Visit 2 (baseline) and Visit 5 (Week 12), using an electronic capture device. The bladder diary may be completed over a weekend, if this is more convenient for the subject. Completion of the bladder diary prior to Visit 2 (baseline) should be begun only after previous treatment with prohibited concomitant medications has undergone a minimum washout appropriate to the drug so any clinical effect is at a minimum eg, 3 day minimum washout for oxybutynin, 7 day minimum washout for darifenacin and solifenacin. Daily micturition or catheterization frequency, volume of urine from each micturition or catheterization (for one of the days), incontinence episodes and urgency episodes (if appropriate) will be recorded. Urinary urgency is defined according to the International Children's Continence Society standards as the sudden and unexpected experience of an immediate need to void (Neveus, et al, 2006).[3]

A proxy (eg, parent or teacher) may assist with completion of the diary if necessary. Contact should be made approximately 1 week prior to Visit 2 (unless the randomization visit occurs within 1 week of screening (V1)) and also prior to Visit 5, to remind the subject to complete the bladder diary and to review instructions on proper completion. Bladder diary completion may be verified via remote review of electronic data.

## 7.2. Safety Assessments

### 7.2.1. Vital Signs

Blood pressure, temperature and pulse rate should be measured at Visit 1, Visit 2, Visit 3, Visit 5 and Visit 7. This schedule of measurements should provide adequate indication of any clinically relevant changes. However, if vital signs show a clinically relevant change from baseline, then safety monitoring will occur at a minimum of monthly intervals, or more frequently as clinically appropriate, until the abnormality resolves. The measured results will be assessed in the context of age appropriate norms.

Temperature may be taken via oral, tympanic or axillary routes as per local accepted practice. Digital devices are permitted; however, mercury thermometers should not be used. The same method should be used for the subject throughout the study.

Blood pressure should be measured using a pediatric or appropriately sized sphygmomanometer in the sitting/resting position with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg. The same arm (preferably the dominant arm) will be used throughout the study.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring BP and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

### 7.2.2. Physical Examination

A physical examination will be performed at V1/Screening, and will include the following systems:

- General appearance (including weight);
- Skin;
- Head, eyes, ears, nose, and throat; including visual acuity and accommodation (see Section 7.2.4).
- Respiratory;
- Cardiovascular;

- Gastrointestinal;
- Musculoskeletal;
- Neurological.

If physical examinations show a clinically relevant change from baseline, then safety monitoring will occur at a minimum of monthly intervals, or more frequently as clinically appropriate, until the abnormality resolves. Any clinically significant negative changes from the entry examination will be recorded as adverse events.

### 7.2.3. Weight Measurements

Weight will be recorded at Screening and used to assess eligibility, to determine which cohort the subject should be enrolled into and for stratification purposes (for Cohort 1, >25 Kg only). Subsequently weight will be recorded at Visit 3, Visit 5, and Visit 7. All weight measurements should be standardized using the same equipment and measuring technique for an individual subject. Any clinically significant change in weight should be reported as an adverse event.

### 7.2.4. Visual Acuity and Accommodation

Visual acuity will be assessed for each eye using the Snellen method, using an optotype that is appropriate to the child's intellectual development at Visit 2, Visit 5, and Visit 7.

Amplitude of accommodation will be assessed by the push up test to assess minimum focusing distance at Visit 2, Visit 5, and Visit 7. The subject will focus on a single letter of the 20/40 line of an eye chart (appropriate optotype) and this will be moved slowly toward the subject until it blurs. At this point the distance from eye to letter will be measured. An attempt will be made to record 3 measurements and entered in the eCRF.

For both visual acuity and accommodation assessments the same optotype will be used for a specific subject throughout the study to ensure standardization and validity.

### 7.2.5. Electrocardiogram

ECGs should be performed after the subject has rested quietly for at least 10 minutes. A single 12-lead ECG will be obtained on all subjects at screening (V1).

The ECG at the screening visit should have no clinically significant abnormalities for the subject to be included in the study.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve consistent ECG recordings. The ECG will be reviewed by a central reader for any clinically significant abnormality.

### 7.2.6. Post-Void Residual (PVR) Urine Volume

PVR urine volume in subjects not performing CIC will be assessed using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. If at screening, the measured volume is higher than 20 ml (see exclusion criterion 13), this should be confirmed by one repeated reading. The subject will be asked to void again. Repeat PVR assessment should be made as soon as possible and no more than 5 minutes, after the second void. If the volume present in the bladder is still above the limit the subject should not be included.

Assessment of PVR in subjects performing CIC should also be carried out in the event that they experience >1 UTI during the study.

PVR measurements should be performed at V1 (Screening), V2 (Baseline), V3 (W4), V5 (W12), and V7 (W24).

### 7.2.7. Clinical Laboratory Evaluation

Safety laboratory tests will be performed at Visit 1 (Screening) and additional visits as below, or as needed to follow-up on significant findings (Section 8.5.2).

**Safety Laboratory (see Appendix 2)**

| Hematology – V1, V5, V7 | Chemistry - V1, V5, V7 | Urinalysis – V1, V3, V5, V7 | Other |
|---|---|---|---|
| Hemoglobin<br>Hematocrit<br>RBC count<br>Platelet count<br>WBC count with differential as below:<br>Total neutrophils (Abs)<br>Eosinophils (Abs)<br>Monocytes (Abs)<br>Basophils (Abs)<br>Lymphocytes (Abs) | GOT (AST)<br>GPT (ALT)<br>GGT<br>Total and direct bilirubin<br>Alkaline phosphatase<br>LDH<br>CPK<br>BUN<br>Creatinine[c]<br>Uric acid<br>Total protein<br>Sodium<br>Potassium<br>Chloride<br>Albumin<br>Corrected calcium<br>Bicarbonate<br>Phosphorus<br>Glucose (non fasting) | Urine will be tested for the following using a urine dipstick:<br>pH<br>Specific gravity<br>Leukocyte esterase<br>Nitrites<br>Glucose<br>Protein<br>Blood<br>Ketones<br><br>Urine microscopy, culture and sensitivity[a] | Pregnancy Test[b] (serum V1, urine at subsequent Visits, 2, 3, 5, and 7)<br><br>Unanonymized pharmacogenomic sample (V3 and V5)[d]<br><br>PK sample (V3 only)[d] |

[a] Urine microscopy, culture and sensitivity to be performed in the event of the presence of symptoms (eg, fever, flank pain), positive leucocytes and/or nitrites on urinalysis, or if the subject has a documented history of vesicoureteral reflux (VUR).
Subjects who are found to have an active UTI during screening as defined in exclusion criterion 12 may continue screening activities on resolution of symptoms or treatment of the UTI to the satisfaction of the treating physician.
[b] Females of childbearing potential only (≥9 years old or have experienced menarche, whichever is earlier). Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
[c]When indicated, the investigator may request calculation of an estimated GFR using the Schwartz equation GFR = (k x H)/Cr where k = constant, H = Height (length) and Cr = Creatinine. In this case, the laboratory will need to be provided with the subject's height in cm.
[d] At V3 PG and PK samples are for fesoterodine group subjects only. At V5 (or early withdrawal from the active comparator/efficacy phase), only subjects who were on oxybutynin who will continue into the safety extension phase and who do not have prior laboratory documentation of their CYP2D6 genotype (PG).

### 7.2.8. Childhood Behavior Checklist (CBCL) (Appendix 4)

The CBCL is a questionnaire by which a child's problem behaviors and competencies can be assessed. This instrument will be completed by the parent or caregiver. The CBCL can also be used to measure a child's change in behavior over time or following a treatment. The first section of this questionnaire consists of 20 competence items and the second section consists of 120 items on behavior or emotional problems. For the purpose of this trial, the parent or caregiver, should preferably be the same person at each visit, and will be asked to complete 113 items on behavior and emotional problems. The parent or caregiver will be asked to describe their child as of 'now'.

The CBCL will be completed at Visit 2, Visit 5 and Visit 7.

### 7.2.9. Grooved Pegboard Test (GPT)

The Grooved Pegboard Test is a manipulative dexterity test that assesses psychomotor speed, fine motor control, and rapid-visual motor coordination. It consists of a small board of 25 holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the hole before they can be inserted. Time to completion, number of pegs dropped, and number of pegs placed correctly are scored.

The GPT will be assessed at Visit 2, Visit 5 and Visit 7.

### 7.2.10. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, before investigational product administration at the baseline visit and at the end of treatment visit (both urine). A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at Visits 3 and 5, and 7 at the end of the treatment to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

### 7.3. Pharmacokinetic Assessments

The study drug dose on the day of Visit 3 is to be administered at the clinic, when possible. Subjects will be asked to maintain consistency of dosing and to record the dosing times of fesoterodine on the 3 days prior to Visit 3. The actual dates and times of blood sample collection as well as the last three doses of fesoterodine will be recorded in the CRF. Subjects randomized to treatment with oxybutynin (in Cohort 1, >25 kg) will not be required to provide blood samples for pharmacokinetic assessment.

#### 7.3.1. Plasma for Analysis of 5-HMT

At Visit 3 (Week 4), blood samples (2 ml each) to provide approximately 1 mL of plasma for the analysis of 5-HMT will be collected into appropriately labeled tubes containing sodium heparin as anticoagulant. Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C or lower within 1 hour of collection.

A maximum of three (3) pharmacokinetic blood samples will be collected from each subject assigned to receive fesoterodine treatment. Sampling times for the PK samples will be determined on an individual subject basis, using the following general guidance:

- If the dose is administered at the clinic, a blood sample will be obtained just prior to dose administration.
- If the dose is taken up to 3 hours before coming to the clinic, a blood sample will be obtained just after arrival at the clinic.
- One blood sample will be obtained from each subject at about 5 hours (4-6 hrs) post-dose.
- When it is possible for a subject to remain at the clinic, a blood sample may be drawn 8-10 hours after dose administration.

Samples may be used for future metabolite identification and/or further evaluation of the bioanalytical method, such as assay reproducibility. No additional samples are required for this testing, and all samples will be discarded following analysis. These data will be used for internal exploratory purposes and will not be included in the clinical report.

Samples will be analyzed for 5-HMT (also referred to as SPM7605) using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method in compliance with Pfizer standard operating procedures.

#### 7.3.2. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

### 7.4. Pharmacogenomics Evaluations

Variation in the CYP2D6 gene plays a role in metabolism of active metabolite (5-HMT) of fesoterodine. The alleles which will be genotyped are *3, *4, *5, *6, *7, *8, *10, *14, *17, *18, *21, *36, *41 and duplication. Homozygous or heterozygous combinations of *3, *4, *5, *6, *7, *8, *14, *17, *18, and *21 will be classified as poor metabolizer (PM) of CYP2D6. Other genotypes will be classified as extensive metabolizer (EM).

For those subjects who are randomized to fesoterodine and who do not have sufficient laboratory documentation, a 2-ml whole blood sample will be collected for CYP2D6 genotype analysis. All samples will be discarded following analysis. Subjects who have prior laboratory documentation of their CYP2D6 genotype will not be required to submit a blood sample for pharmacogenomics. Subjects randomized to treatment with oxybutynin will also not be required to provide a sample for pharmacogenomic assessment, unless they continue in the fesoterodine safety extension.

#### 7.4.1. Shipment of Pharmacogenomics Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

### 7.5. Dosing Log

A dosing log should be completed by the subject or proxy, and the total number of tablets/capsules taken, time of dose, for subjects ≤ 25 kg whether the dose of fesoterodine was swallowed or sprinkled, as well as the reason for any change, recorded on a daily basis, using an electronic capture device. The dosing log should be completed every day. A proxy (eg, parent) may assist with completion of the dosing log if necessary.

Contact should be made with the subject's parent/guardian (caregiver) at Week 1 to verify that they have correctly understood their dose regimen and to remind them to complete their daily dosing log if needed. Evaluation of the dosing log may be performed via remote electronic review. The device will need to be reset at Visits 2 and 5, or in the event of early termination from oxybutynin treatment (in Cohort 1, >25 kg only), this will need to be reset at start of the fesoterodine dosing in the safety extension phase.

The time of the last three doses of fesoterodine prior to V3, and the time of the last dose of fesoterodine and oxybutynin prior to V5 should be captured on the CRF.

## 8. ADVERSE EVENT REPORTING

### 8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

### 8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides their assent and the legal representative provides their informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

### 8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;

- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breast-feeding;
- Medication error;
- Occupational exposure.

### 8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or;
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or;
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or;
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

### 8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death.

- Is life-threatening (immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### 8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on Serious Adverse Event Reporting Requirements).

### 8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

- For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

**Concurrent with**

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/INR and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

### 8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;

- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

### 8.7. Severity Assessment

**TABLE 1: SEVERITY ASSESSMENT**

| If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows: | |
|---|---|
| MILD | Does not interfere with subject's usual function. |
| MODERATE | Interferes to some extent with subject's usual function. |
| SEVERE | Interferes significantly with subject's usual function. |

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

### 8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (Reporting Requirements, Section 8.12). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

### 8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) after discontinuing or having been directly exposed to the investigational product.

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event Form and Exposure in Utero (EIU) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EIU Form.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.

- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to the exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Exposure in Utero Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the Exposure in Utero Form that the subject was given this letter to provide to his partner.

### 8.10. Withdrawal Due to Adverse Events (See section on Subject Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

## 8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events.

## 8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

### 8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast-feeding cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

### 8.12.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

### 8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## 9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan, which will be dated and maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

As the dosing of lighter subjects is dependent on the availability of an age-appropriate Beads-in-Capsule formulation, in the event that it is not possible to develop an age-appropriate formulation, then lighter subjects will not be dosed; the end of the trial will be defined by the completion of the heavier >25 Kg cohort and the analyses specified below for the lighter cohort (Cohort 2) will not be performed.

### 9.1. Sample Size Determination

*Cohort 1 (>25 kg)*

A sample size of 33 evaluable subjects per group is sufficient to give a power of at least 90% to detect a change from baseline of 70 mL in the primary endpoint, maximum cystometric capacity (MCC), when the standard deviation of the change from baseline is 120 mL. This calculation assumes the testing will be performed at a two-sided 5% significance level and is based on results observed from the two highest dose periods (each 4 weeks) in previous tolterodine neurogenic bladder studies 583E-URO-0581-001, 583E-URO-0581-002 and 583-URO-0581-003, as well as published data from studies of oral oxybutynin in neurogenic bladder subjects. An oxybutynin active comparator arm will enable comparisons between fesoterodine and oxybutynin to be made; therefore a sufficient number of subjects will be randomized into Cohort 1 to ensure a total of approximately 99 subjects (33 evaluable subjects per arm) are evaluable at Week 12.

This sample size will also provide a 2-sided 95% confidence interval for the change from baseline in MCC of approximately ± 70 mL around the point estimate for the difference between each fesoterodine arm and oxybutynin, with 90% coverage probability. Using this estimation approach, these confidence intervals will be used to assess the comparability of each fesoterodine dose and oxybutynin.

*Cohort 2 (≤25 kg)*

A sample size of approximately 25 evaluable subjects per arm will provide a 2-sided 95% confidence interval for the change from baseline in maximum cystometric capacity (MCC) of approximately ± 55 mL around the point estimate for the mean, with 80% coverage probability. This assumes a standard deviation of 120 mL. This is based on results observed

from the two highest dose periods (each 4 weeks) in previous tolterodine neurogenic bladder studies 583E-URO-0581-001, 583E-URO-0581-002 and 583-URO-0581-003, as well as published data from studies of oral oxybutynin in neurogenic OAB patients. It is planned that a sufficient number of subjects will be randomized into this cohort to ensure a total of approximately 50 subjects (25 evaluable subjects per arm) are evaluable at Week 12.

## 9.2. Efficacy Analysis

### 9.2.1. Efficacy Analysis Sets

The following efficacy analysis sets will be determined separately for each cohort.

#### 9.2.1.1. Full Analysis Set (FAS)

The Full Analysis Set for each cohort will include all subjects who have been randomized and received at least one dose of study medication and have provided baseline primary endpoint data.

#### 9.2.1.2. Per Protocol Analysis Set (PPAS)

The Per Protocol Analysis Set for each cohort will include all subjects who have completed the active comparative phase of the study, and who have not violated any of the inclusion/exclusion criteria or deviated from the protocol in a way that could affect the efficacy outcome of the study.

The PPAS for each cohort will be defined prior to unblinding the study.

### 9.2.2. Analysis of Primary Endpoint

#### 9.2.2.1. Cohort 1 (>25 kg)

Change from baseline to Week 12 in the primary endpoint will be analysed using an ANCOVA including terms for treatment group, baseline (for the endpoint being analyzed) and weight. The Least Squares mean change from baseline for each treatment group, standard error, 95% confidence intervals and p-values associated with the Least Squares mean changes from baseline will be presented.

All endpoints will also be summarized descriptively for each treatment group, by timepoint, using: N, mean, standard deviation, median, minimum and maximum. Should any of the assumptions of the analysis methods not be adequately met, alternative procedures will be used and fully documented.

The following primary comparisons of interest will be assessed:

- Change from Baseline to Week 12 for fesoterodine 4 mg.
- Change from Baseline to Week 12 for fesoterodine 8 mg.

The Least Squares means and 95% confidence intervals for the difference between each fesoterodine dose group and oxybutynin will also be calculated.

The following secondary comparisons will be assessed using 95% confidence intervals for the difference between treatment means (for the change from baseline to Week 12):

- Fesoterodine 4 mg vs Oxybutynin.
- Fesoterodine 8 mg vs Oxybutynin.

As these secondary comparisons are based on an estimation approach, no formal statistical hypothesis testing will be performed. Conclusions will be based on point estimates and confidence intervals.

The primary analysis will be based on the Cohort 1 Full Analysis Set (FAS1). The secondary analysis set will be the Cohort 1 Per Protocol Analysis Set (PPAS1).

For the PPAS analysis no imputation techniques for missing data will be employed. For the FAS analysis a Baseline Observation Carried Forward (BOCF) and a Last Observation Carried Forward (LOCF) algorithm will be used for missing data.

Data from the active comparator phase for this cohort may be summarised, analysed and reported after all subjects in this cohort have either completed or withdrawn prior to the Week 12 visit (ie, prior to formal completion of the study). The results of these analyses will be available to limited members of the study team as a management tool in order to aid decision making, and may also be shared with regulators in order to facilitate timely discussion of the overall program; they will not be used to stop or modify the design of the study.

#### 9.2.2.2. Cohort 2 (≤25 kg)

Change from baseline to Week 12 in the primary endpoint will be analyzed using an ANCOVA including terms for treatment group and baseline (for the endpoint being analyzed). The Least Squares mean change from baseline for each treatment group, standard error and 95% confidence intervals associated with the Least Squares mean changes from baseline will be presented.

All endpoints will also be summarized descriptively for each treatment group, by timepoint, using: N, mean, standard deviation, median, minimum and maximum. Should any of the assumptions of the analysis methods not be adequately met, alternative procedures will be used and fully documented.

The following primary comparisons of interest will be assessed:

- Change from Baseline to Week 12 for fesoterodine 2 mg.
- Change from Baseline to Week 12 for fesoterodine 4 mg.

As these comparisons are based on an estimation approach, no formal statistical hypothesis testing will be performed. Conclusions will be based on point estimates and confidence intervals.

The primary analysis will be based on the Cohort 2 Full Analysis Set (FAS2). The secondary analysis set will be the Cohort 2 Per Protocol Analysis Set (PPAS2).

For the PPAS analysis no imputation techniques for missing data will be employed. For the FAS analysis a Baseline Observation Carried Forward (BOCF) and a Last Observation Carried Forward (LOCF) algorithm will be used for missing data.

Data from the efficacy phase for this cohort may be summarized, analyzed and reported after all patients in this cohort have either completed or withdrawn prior to the Week 12 visit (ie, prior to formal completion of the study). The results of these analyses will be available to limited members of the study team as a management tool in order to aid decision making, and may also be shared with regulators in order to facilitate timely discussion of the overall program; they will not be used to stop or modify the design of the study.

### 9.2.3. Analysis of Secondary Endpoints

All secondary endpoints will be analysed using the same methods as the primary endpoint for each cohort.

### 9.2.4. Analysis of Other Endpoints

Plasma concentrations of 5-HMT will be listed and summarized using descriptive statistics, by timepoint and treatment group.

The population PK modeling approach will be used to analyze the plasma concentration-time data following fesoterodine administration for the estimation of population PK parameters (CL/F, Ka and Vd) of 5-HMT in pediatric subjects in this study. Confidence intervals will be computed for means and variances of estimates. Using NONMEM, the first-order or first order conditional estimation methods will be employed for all model building. Individual estimates of PK parameters will be obtained using POSTHOC, an empirical Bayesian Estimation Method. Population mean estimates for the pharmacokinetic parameters will be obtained by fitting the pharmacokinetic and variance models to the whole data set of all individuals. The inter-subject variability will be estimated and 95% confidence intervals will be reported for all population parameter estimates. For the residual variability, various models will be fitted, including but not restricted to additive and proportional models. Adequacy of model fitting will be judged by the objective function as well as goodness of fit plots and parameter precision estimates. Exploratory analyses will be performed to investigate the effect of covariates including, but not limited to age, weight, CYP2D6 status, and sex. An analysis plan describing the details of the model building, covariate assessment and model validation will be provided separately.

### 9.3. Safety Analysis

The Safety Analysis Set will be defined separately for each cohort and consists of all randomized subjects who have received at least one dose of study medication in the relevant phase of the study.

For each cohort, results from the safety assessments and any adverse events will be presented in tabular and/or graphical format adhering to current Pfizer Data Standards. These presentations will be split by treatment group, and produced separately for the active comparator/efficacy phase and the safety extension phase. Safety endpoints such as vital signs, laboratory evaluations, weight, PVR, vision testing and CBCL/GPT results will be presented descriptively by treatment group. Adverse event incidence rates will be compared descriptively between treatment arms. An evaluation of withdrawal rates and time to withdrawal will be performed.

### 9.4. Blinded Interim Analysis for Sample Size Re-estimation.

A blinded interim analysis may be performed after approximately 50% of randomized subjects in Cohort 1 have completed the active comparator phase of the study and provided data for the primary endpoint (including the corresponding baseline value) as a tool to reassess the sample size. The sample size will be recalculated based on the variability of the primary endpoint obtained from this analysis. Even though this is an open label study, data utilized in this interim analysis will remain blinded to treatment allocation to minimize bias. Based on this, the study statistician and clinician will assess whether an adjustment to the sample size is required.

These results will not be used to modify the design of the study, other than a potential adjustment to the sample size. No adjustment will be made to the nominal p-values to account for this analysis. The results of this analysis will not be made available to the investigator and site staff, other than to inform them of any adjustment to the sample size that is recommended. A similar blinded interim analysis may be performed after approximately 50% of randomized subjects in Cohort 2 have completed the efficacy phase of the study.

### 9.5. External Data Monitoring Committee

This study will use an External Data Monitoring Committee (EDMC) for the purpose of protecting the safety of subjects by regular independent assessment of risk/benefit during the conduct of the study (for each cohort separately as well as combined). The recommendations made by the EDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

The EDMC will meet at specified intervals during the study to assess its progress including the safety data and/or critical efficacy endpoints. Safety data will include assessment of adverse events, vision testing, CBCL/GPT assessments, vital signs including heart rate, incidence of urinary tract infection (as evidenced by urinalysis, urine microscopy and

culture), clinical laboratory evaluations in the context of age-appropriate norms, with particular reference to liver function tests and renal chemistry, and post-void residual volume (PVR) in subjects not performing CIC, or with >1 urinary tract infection (UTI) during the study.

Assessment of adverse events of particular interest will include, but not be limited to, anticholinergic effects such as dry mouth, dry eyes and constipation, CNS effects such as behavioral changes (eg, aggression), decreased cognitive function, headache, seizures, somnolence and visual effects such as accommodation disorder, blurred vision, and amblyopia.

The remit of the EDMC will be to recommend whether to continue or modify the study. In the event that a negative benefit-risk is determined, the EDMC may recommend that the study (or recruitment to a particular cohort) be terminated. The EDMC will be advisory to the sponsor, Pfizer Inc. The sponsor will promptly review the EDMC recommendations, and will make decisions regarding accepting, modifying or rejecting those recommendations. The final decisions regarding trial continuation, modification or termination will be made by the sponsor.

Full technical details for the EDMC, including its primary responsibilities, relationship with other trial components, membership, timing of meetings, and rules will be provided in the EDMC Charter, which will be drawn up by the sponsor study team and agreed to by the EDMC. All members included in an EDMC must have acceptable conflict of interest status and a contract should be in place before the work commences.

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

# 11. DATA HANDLING AND RECORD KEEPING

## 11.1. Case Report Forms / Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

## 11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## 12. ETHICS

### 12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

### 12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association, 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

### 12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by an alpha-numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legal representative, are fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative, and subject assent when appropriate, before any study-specific activity is performed. The investigator will retain the original of each subject's or the subject's legal representative signed consent document. Informed consent should be obtained from the parent(s) or legal representative before assent is sought.

An assent from the subject will be obtained in addition to the consent when appropriate, and when the potential subject is capable of providing assent. The determination of appropriateness and capacity is made by the investigator and/or the relevant IRB or IEC, and should take into account the age, maturity, and psychological state of the potential subject. Assent is not required if the investigator and/or the IRB/IEC determine that the capability of the child or adolescent subject is so limited that they cannot provide assent.

When applicable, full informed consent from “emancipated minors” is both necessary and sufficient, rather than assent plus the consent of a legally acceptable representative or representatives.

If a minor becomes of age following assent and enrolment in the study, a consent must be signed once the subject turns legal age, based on local requirements.

### 12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures. Other methods, for example, increasing awareness of the study through patient associations, may be used as appropriate, and subject to approval by ethics committees.

### 12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

## 13. DEFINITION OF END OF TRIAL

### 13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

### 13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit.

## 14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of fesoterodine at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a time period set by Pfizer. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## 15. PUBLICATION OF STUDY RESULTS

### 15.1. Communication of results by Pfizer:

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer registers study protocols and posts Basic Results on ClincialTrials.gov for Pfizer-sponsored interventional studies in human subjects that evaluate the safety and/or efficacy of a Pfizer product

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

### 15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

## 16. REFERENCES

1. Bauer SB, Koff SA, Jayanthi VR. Voiding dysfunction in children: neurogenic and nonneurogenic. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology. 8th ed. Saunders; 2002: p. 2231-61.

2. Aslan AR, Kogan BA. Conservative management in neurogenic bladder dysfunction. Curr Opin Urol 2002; 12: 473-77.

3. Neveus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006; 176: 314-24.

4. Coward RJM, Saleem MA. The neuropathic bladder of childhood. Current Paediatrics 2001;11:135-42.

5. Kennelly MJ, DeVoe WB. Overactive bladder: pharmacologic treatments in the neurogenic population. Rev Urol 2008; 10(3):182-91

## Appendix 1. Examples of CYP3A4 Inducers and Potent CYP3A4 Inhibitors

Potent CYP3A4 inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the trial, as well as medications capable of inducing CYP3A4 enzyme metabolism are prohibited.

The following table provides examples of such medications. The lists are provided for your reference only and are not intended to be all-inclusive. Please consult a member of the study team for further clarification if necessary.

| **CYP3A4 Inducers** | **Potent CYP3A4 Inhibitors** |
|---|---|
| efavirenz<br>nevirapine<br>barbiturates<br>carbamazepine<br>glucocorticoids<br>modafinil<br>oxcarbazepine<br>phenobarbital<br>phenytoin<br>pioglitazone<br>rifabutin<br>rifampin<br>St. John's wort<br>Troglitazone | indinavir<br>nelfinavir<br>ritonavir<br>clarithromycin<br>itraconazole<br>ketoconazole<br>nefazodone<br>saquinavir<br>telithromycin |

## Appendix 2. Total Volume of Trial-Related Blood Loss

| BLOOD TEST | | FESOTERODINE 2, 4 or 8 mg | | | | OXYBUTYNIN | |
|---|---|---|---|---|---|---|---|
| | | Volume of whole blood | | | | Volume of whole blood | |
| **Test panel** | **Test** | **Visit 1 Screening Week 0** | **Visit 3 Week 4** | **Visit 5 Week 12** | **Visit 7 Week 24** | **Visit 1 Screening** | **Visit 5 Week 12** |
| **Hematology** | Hemoglobin<br>Hematocrit<br>RBC count<br>Platelet count<br>WBC count with differential of total neutrophils, eosinophils, monocytes, basophils, lymphocytes | 2 ml | N/A | 2 mL | 2 mL | 2 ml | 2 ml |
| **Chemistry** | GOT (AST)<br>GPT (ALT)<br>GGT<br>Total and direct bilirubin<br>Alkaline phosphatase<br>Lactate dehydrogenase (LDH)<br>Creatine phosphokinase (CPK)<br>Blood urea nitrogen (BUN)<br>Creatinine<br>Uric acid<br>Total protein<br>Albumin<br>Sodium<br>Potassium<br>Chloride<br>Bicarbonate<br>Phosphorus<br>Corrected calcium<br>Glucose (non-fasting)<br><br>Serum pregnancy test (in females of childbearing potential only)[a] | 3.5 ml | N/A | 3.5 mL | 3.5 mL | 3.5 ml | 3.5 ml |
| **Pharmacokinetic** | 5-HMT | N/A | 6 mL | N/A | N/A | N/A | N/A |
| **Pharmacogenomic** | CYP2D6 | N/A | 2 mL | N/A | N/A | N/A | 2 mL |
| **Total blood volume** | Total volume per visit | 5.5 ml | 8 mL | 5.5 ml[b] | 5.5 mL | 5.5 ml | 7.5 ml |
| | Total volume over study | 24.5 mL[b] | | | | 13 mL | |

N/A - not applicable. Additional blood samples may be taken as needed to follow-up on significant findings, or as clinically indicated. The total volume does not include discarded blood from predraws used to remove fluid from flushed catheters at Visit 3. The discarded volume is not anticipated to exceed 1.65 ml based on 3 draws using winged infusion (butterfly) set with a priming volume of 0.55 ml (23G, ¾ inch, 12 inch tubing).

[a] Serum pregnancy test at Screening (Visit 1) only (urine testing at subsequent visits)

[b] For fesoterodine treatment groups, if no PG sample is required (due to prior genotyping), total blood volume at Visit 3 = 6 ml, total blood volume over the study = 22.5 mL.

| | **Guidelines[a]** | **A0221047 blood loss volume (volume including discarded blood[d])** |
|---|---|---|
| Maximum total volume at a single time | 20 ml[b] | 13.5 ml (16.25 ml) |
| Maximum total volume in a 4 week period | 60 ml[c] | 13.5 ml (16.25 ml) |
| Maximum *possible* total volume in a 4 week period (assuming subject withdraws prior to Visit 5, and within 4 weeks of Screening at Visit 1) | 60 ml | 19 ml (22.3 ml) |

[a] As per *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (Section 13.2)* http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf. Accessed 24 Nov 2010: Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time. Subjects weighing less than 17 kg will be very unusual, especially for this population, and the breach of maximum guidelines volume is minor if it does happen, and it should be possible to stay within guideline limits by a very minor reduction in draw volume that does not affect ability to analyse.
[b] 1 % is 0.8 ml/kg = 0.8 ml x 25 kg = 20 ml at single time assuming minimum body weight of 25 kg and total volume of blood of 80 ml/kg body weight; for a 17 kg subject the volume is 13.6 mL,
[c] 3% is 2.4 ml/kg = 2.4 ml x 25 kg = 60 ml in a 4 week period assuming minimum body weight of 25 kg and total volume of blood of 80 ml/kg body weight;for a 17 kg subject the volume is 40.8 mL
[d] Assuming that predraws (to remove fluid from flushed catheters) are performed between each sample taken and based on a winged infusion (butterfly) set with a priming volume of 0.55 ml (23G, ¾ inch, 12 inch tubing).

## Appendix 3. Washout Times for Anticholinergic Medications

| Generic name | Example Trade names | Elimination half life* | Minimum recommended washout period |
|---|---|---|---|
| Tolterodine IR | Detrol/Detrusitol | EMs: ~2 hrs<br>PMs: ~10 hrs | 3 days |
| Tolterodine XL | Detrol/Detrusitol | EMs: ~7 hrs<br>PMs: ~18 hrs | 3 days |
| Oxybutynin IR | Cystrin | 2-3 hrs | 3 days |
| Oxybutynin XL | Lyrinel XL<br>Ditropan XL (US) | 12-13 hr | 3 days |
| Darifenacin | Emselex | 13 - 19 hrs | 7 days |
| Solifenacin | Vesicare | 45 - 68 hrs | 7 days |
| Fesoterodine | Toviaz | ~7 hrs | 3 days |
| Propiverine | Detrunorm | 20 hrs | 7 days |
| Trospium IR | Sanctura | 18 hrs | 3 days |
| Trospium SR | Sanctura XR | 36 hrs | 7 days |

*Data from the respective drug labels

# Appendix 4. Child behavior Checklist (CBCL)

***Please print. Be sure to answer all items.***

Below is a list of items that describe children and youths. For each item that describes your child ***now***, please circle the ***2*** if the item is ***very true or often true*** of your child. Circle the ***1*** if the item is ***somewhat or sometimes true*** of your child. If the item is ***not true*** of your child, circle the ***0***. Please answer all items as well as you can, even if some do not seem to apply to your child.

**0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | 1. Acts too young for his/her age | **0** | **1** | **2** | 17. Daydreams or gets lost in his/her thoughts |
| **0** | **1** | **2** | 2. Drinks alcohol without parents' approval (describe):_____ _____ | **0** | **1** | **2** | 18. Deliberately harms self or attempts suicide |
| **0** | **1** | **2** | 3. Argues a lot | **0** | **1** | **2** | 19. Demands a lot of attention |
| **0** | **1** | **2** | 4. Fails to finish things he/she starts | **0** | **1** | **2** | 20. Destroys his/her own things |
| **0** | **1** | **2** | 5. There is very little he/she enjoys | **0** | **1** | **2** | 21. Destroys things belonging to his/her family or others |
| **0** | **1** | **2** | 6. Bowel movements outside toilet | **0** | **1** | **2** | 22. Disobedient at home |
| **0** | **1** | **2** | 7. Bragging, boasting | **0** | **1** | **2** | 23. Disobedient at school |
| **0** | **1** | **2** | 8. Can't concentrate, can't pay attention for long | **0** | **1** | **2** | 24. Doesn't eat well |
| **0** | **1** | **2** | 9. Can't get his/her mind off certain thoughts; obsessions (describe): _____ _____ | **0** | **1** | **2** | 25. Doesn't get along with other kids |
| **0** | **1** | **2** | 10. Can't sit still, restless, or hyperactive | **0** | **1** | **2** | 26. Doesn't seem to feel guilty after misbehaving |
| **0** | **1** | **2** | 11. Clings to adults or too dependent | **0** | **1** | **2** | 27. Easily jealous |
| **0** | **1** | **2** | 12. Complains of loneliness | **0** | **1** | **2** | 28. Breaks rules at home, school, or elsewhere |
| **0** | **1** | **2** | 13. Confused or seems to be in a fog | **0** | **1** | **2** | 29. Fears certain animals, situations, or places, other than school (describe):_____ _____ |
| **0** | **1** | **2** | 14. Cries a lot | **0** | **1** | **2** | 30. Fears going to school |
| | | | | **0** | **1** | **2** | 31. Fears he/she might think or do something bad |
| **0** | **1** | **2** | 15. Cruel to animals | **0** | **1** | **2** | 32. Feels he/she has to be perfect |
| **0** | **1** | **2** | 16. Cruelty, bullying, or meanness to others | **0** | **1** | **2** | 33. Feels or complains that no one loves him/her |

***Please print. Be sure to answer all items.***

**0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | 34. Feels others are out to get him/her | **0** | **1** | **2** | 56. Physical problems ***without known medical cause:*** |
| **0** | **1** | **2** | 35. Feels worthless or inferior | **0** | **1** | **2** | a. Aches or pains (***not*** stomach or headaches) |
| **0** | **1** | **2** | 36. Gets hurt a lot, accident–prone | **0** | **1** | **2** | b. Headaches |
| **0** | **1** | **2** | 37. Gets in many fights | **0** | **1** | **2** | c. Nausea, feels sick |
| **0** | **1** | **2** | 38. Gets teased a lot | **0** | **1** | **2** | d. Problems with eyes (***not*** if corrected by glasses) (describe):_____ _____ |
| **0** | **1** | **2** | 39. Hangs around with others who get in trouble | **0** | **1** | **2** | e. Rashes or other skin problems |
| **0** | **1** | **2** | 40. Hears sound or voices that aren't there (describe):_____ _____ | **0** | **1** | **2** | f. Stomachaches |
| **0** | **1** | **2** | 41. Impulsive or acts without thinking | **0** | **1** | **2** | g. Vomiting, throwing up |
| **0** | **1** | **2** | 42. Would rather be alone than with others | **0** | **1** | **2** | h. Other (describe):_____ _____ |
| **0** | **1** | **2** | 43. Lying or cheating | **0** | **1** | **2** | 57. Physically attacks people |
| **0** | **1** | **2** | 44. Bites fingernails | **0** | **1** | **2** | 58. Picks nose, skin, or other parts of body (describe): _____ _____ |
| **0** | **1** | **2** | 45. Nervous, highstrung, or tense | **0** | **1** | **2** | 59. Plays with own sex parts in public |
| **0** | **1** | **2** | 46. Nervous movements or twitching (describe):_____ _____ _____ | **0** | **1** | **2** | 60. Plays with own sex parts too much |
| **0** | **1** | **2** | 47. Nightmares | **0** | **1** | **2** | 61. Poor school work |
| **0** | **1** | **2** | 48. Not liked by other kids | **0** | **1** | **2** | 62. Poorly coordinated or clumsy |
| **0** | **1** | **2** | 49. Constipated, doesn't move bowels | **0** | **1** | **2** | 63. Prefers being with older kids |
| **0** | **1** | **2** | 50. Too fearful or anxious | **0** | **1** | **2** | 64. Prefers being with younger kids |
| **0** | **1** | **2** | 51. Feels dizzy or lightheaded | **0** | **1** | **2** | 65. Refuses to talk |
| **0** | **1** | **2** | 52. Feels too guilty | **0** | **1** | **2** | 66. Repeats certain acts over and over; compulsions describe):_____ _____ |
| **0** | **1** | **2** | 53. Overeating | **0** | **1** | **2** | 67. Runs away from home |
| **0** | **1** | **2** | 54. Overtired without good reason | **0** | **1** | **2** | 68. Screams a lot |
| **0** | **1** | **2** | 55. Overweight | **0** | **1** | **2** | 69. Secretive, keeps things to self |

***Please print. Be sure to answer all items.***

**0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | 70. Sees things that aren't there (describe):_____ _____ | **0** | **1** | **2** | 87. Sudden changes in mood or feelings |
| **0** | **1** | **2** | 71. Self-conscious or easily embarrassed | **0** | **1** | **2** | 88. Sulks a lot |
| **0** | **1** | **2** | 72. Sets fires | **0** | **1** | **2** | 89. Suspicious |
| **0** | **1** | **2** | 73. Sexual problems (describe):_____ _____ _____ | **0** | **1** | **2** | 90. Swearing or obscene language |
| **0** | **1** | **2** | 74. Showing off or clowning | **0** | **1** | **2** | 91. Talks about killing self |
| **0** | **1** | **2** | 75. Too shy or timid | **0** | **1** | **2** | 92. Talks or walks in sleep (describe): _____ _____ |
| **0** | **1** | **2** | 76. Sleeps less than most kids | **0** | **1** | **2** | 93. Talks too much |
| **0** | **1** | **2** | 77. Sleeps more than most kids during day and/or night (describe):_____ _____ | **0** | **1** | **2** | 94. Teases a lot |
| **0** | **1** | **2** | 78. Inattentive or easily distracted | **0** | **1** | **2** | 95. Temper tantrums or hot temper |
| **0** | **1** | **2** | 79. Speech problem (describe):_____ _____ | **0** | **1** | **2** | 96. Thinks about sex too much |
| **0** | **1** | **2** | 80. Stares blankly | **0** | **1** | **2** | 97. Threatens people |
| **0** | **1** | **2** | 81. Steals at home | **0** | **1** | **2** | 98. Thumb-sucking |
| **0** | **1** | **2** | 82. Steals outside the home | **0** | **1** | **2** | 99. Smokes, chews, or sniffs tobacco |
| **0** | **1** | **2** | 83. Stores up too many things he/she doesn't need (describe):_____ _____ _____ | **0** | **1** | **2** | 100. Trouble sleeping (describe): _____ _____ |
| **0** | **1** | **2** | 84. Strange behavior (describe): _____ _____ | **0** | **1** | **2** | 101. Truancy, skips school |
| **0** | **1** | **2** | 85. Strange ideas (describe): _____ _____ | **0** | **1** | **2** | 102. Underactive, slow moving, or lacks energy |
| **0** | **1** | **2** | 86. Stubborn, sullen, or irritable | **0** | **1** | **2** | 103. Unhappy, sad, or depressed |

***Please print. Be sure to answer all items.***

**0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | 104. Unusually loud | **0** | **1** | **2** | 111. Withdrawn, doesn't get involved with others |
| **0** | **1** | **2** | 105. Uses drugs for nonmedical purposes (***don't*** include alcohol or tobacco) (describe):_____ _____ | **0** | **1** | **2** | 112. Worries |
| **0** | **1** | **2** | 106. Vandalism | | | | 113. Please write in any problems your child has that were not listed above: |
| **0** | **1** | **2** | 107. Wets self during the day | **0** | **1** | **2** | _____ |
| **0** | **1** | **2** | 108. Wets the bed | **0** | **1** | **2** | _____ |
| **0** | **1** | **2** | 109. Whining | **0** | **1** | **2** | _____ |
| **0** | **1** | **2** | 110. Wishes to be of opposite sex | | | | |

## Appendix 5. Country-specific amendment: France

**In France, the following amendments apply:**

### 4.2 Exclusion criteria

Subjects presenting with any of the following will not be included in the study:

1. Any condition known to affect drug absorption (eg, gastrectomy).

2. History of surgical procedures that could confound study results or increase the risk to subjects, including but not limited to: sphincterotomy, artificial sphincter, implantable stent, bladder augmentation procedures, urinary diversion procedures. Continent diversion procedures eg, Mitrofanoff are permitted.

3. A history of indwelling urinary catheter within 4 weeks of participation in this study. Intermittent catheterization is permitted.

4. Any comorbid condition that, in the opinion of the investigator, would confound study results or increase the risk to subjects eg, current history of bladder calculus.

5. A history of autonomic dysreflexia eg, increased blood pressure with bladder filling or other stimuli.

6. Subjects who have had an endoscopic anti-reflux procedure in the previous 3 months before Visit 2.

7. Subjects with clinically relevant out-of-range values for hematology or serum chemistry as confirmed by blood tests performed at Visit 1, and which require the subject's exclusion in the opinion of the investigator.

8. A 12-lead ECG at screening with clinically significant abnormality.

9. Subjects who present with QTc interval prolongation, personal and family history of QTc interval prolongation, or pre-existing and important cardiac diseases and present a risk of QT interval prolongation (eg, hypokalemia).

10. Unwilling or unable to comply with the Lifestyle guidelines described in this protocol.

11. Subjects required to take or expected to initiate concomitant medications that can interact with the pharmacokinetics and/or pharmacodynamics of fesoterodine or oxybutynin, such as:

    - Potent CYP3A4 inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the trial (Appendix 1).

    - Medications capable of inducing CYP3A4 enzyme metabolism (Appendix 1).

- Drugs for the treatment of overactive bladder (eg, darifenacin, oxybutynin (including intravesical), propiverine, tolterodine, fesoterodine, solifenacin and trospium).

- Treatment with botulinum toxin A within 9 months prior to Visit 2 (baseline).

- Drugs with antispasmodic, parasympathetic, or cholinergic effects. Stable use of desmopressin for enuresis is allowed if established for at least 3 months.

Previous treatment with these medications does not exclude subjects. However, prohibited concomitant medications must have a minimum washout appropriate to the drug so any clinical effect is at a minimum prior to beginning the bladder diary, and baseline urodynamic evaluations (Section 5.6).

12. Intermittent or unstable use of diuretics or alpha blockers, tricyclic antidepressants or any other treatment that may confound the results of the study, within 2 weeks or an appropriate washout period (whichever is longer) prior to starting the bladder diary or during the course of the study. Stable usage/dosage is allowed if established for at least 3 months.

13. Electrostimulation therapy or bladder retraining if started within 30 days of Visit 1 or are expected to start such therapy during the study period. Subjects who are on an established regimen may remain on this for the duration of the study.

14. Subjects with a clinically significant urinary tract infection (UTI) at screening.

Urine microscopy, culture and sensitivity testing will be performed in the event of:

- presence of symptoms (eg, fever, flank pain), or

- positive leucocytes and/or nitrites on urinalysis, or

- if subject has a documented history of vesicoureteral reflux (VUR).

A clinically significant UTI is defined as:

- positive urine culture with a uropathogen (defined as $\geq 10^5$ CFU/ml) and the presence of symptoms, or

- pyuria (defined as >50 white blood cells (WBC)/hpf) and the presence of symptoms, or

- positive urine culture with a uropathogen (defined as $\geq 10^5$ CFU/ml) with or without symptoms in a subject with a documented history of VUR.

Subjects who are found to have an active UTI during screening may continue screening activities on resolution of symptoms or treatment of the UTI to the satisfaction of the treating physician.

15. Subjects not requiring intermittent catheterization who have a post-void residual volume greater than 20 ml as determined by transabdominal ultrasound (eg, bladder scan) immediately after urination. If at screening, the PVR is found to be greater than 20 ml the subject will be asked to void again. Repeat PVR assessment should be made as soon as possible, and no more than 5 minutes, after the second void. Subjects found to have a persistently elevated PVR >20 ml at this visit will be excluded from the study.

16. Subjects with any history of malignancy.

17. Subjects with any condition or at risk of any condition that would contraindicate or warrant precautions for the use of fesoterodine or oxybutynin, including:

    - Hypersensitivity to fesoterodine, tolterodine or oxybutynin.
    - Known history of hypersensitivity to peanut or soya or any of the excipients of the fesoterodine or oxybutynin formulation.
    - Gastric retention.
    - Severely decreased gastrointestinal motility (not under active management).
    - Uncontrolled narrow angle glaucoma.
    - Gastrointestinal obstructive disorders.
    - Myasthenia gravis.
    - Severe hepatic impairment (Child Pugh C).
    - Severe ulcerative colitis.
    - Toxic megacolon.

18. Previously received any investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to Visit 1. Participation in other studies within 4 weeks before the current study begins or during study participation.

19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

20. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

### 6.12 Subject withdrawal

If treatment is inadequate or the subject cannot tolerate the dose of fesoterodine or oxybutynin, consideration should be given to withdrawal.

Subjects who undergo an endoscopic anti-reflux therapy during the study will be withdrawn.

Subjects who withdraw from the oxybutynin treatment arm (Cohort 1, > 25kg) for reasons of toleration, and who fulfill all continuation criteria, may be directly allocated by the investigator to fesoterodine treatment at either 4 mg or 8 mg/day for the remaining 12 week safety extension period if appropriate. All subsequent study visits should be scheduled relative to the start of the extension phase.

Subjects may withdraw from the study at any time at their own, or their legal representative(s) request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s) and electronic diary equipment, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

Subjects in the fesoterodine groups who withdraw prior to Week 4 should have PK samples obtained as per Visit 3.

If a subject withdraws from the study prior to Visit 5 (Week 12), the same assessments as at Visit 5 should be performed if possible. Urodynamic assessment should only be performed in subjects who have been on a stable dose of study medication for at least 2 weeks, and who have not missed any doses in the 3 days prior to the visit.

If a subject withdraws from the study after Visit 5, the same assessments as at Visit 7 (Week 24) should be performed if possible.

Subjects who withdraw early from the study and who have taken at least 1 dose of study medication should also be contacted by telephone approximately 2 weeks after stopping study medication, and have the same assessments performed as at Visit 8 (Week 26).

If the subject withdraws from the study, and they or their legal representative(s) also withdraw consent for disclosure of future information, no further evaluations should be

performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.