CLINICAL PROTOCOL

LONG-TERM EXTENSION STUDY TO EVALUATE THE SAFETY OF FESOTERODINE IN JAPANESE PEDIATRIC SUBJECTS WITH SYMPTOMS OF DETRUSOR OVERACTIVITY ASSOCIATED WITH A NEUROLOGICAL CONDITION (NEUROGENIC DETRUSOR OVERACTIVITY) WHO HAVE COMPLETED 24 WEEKS TREATMENT IN STUDY A0221047

Compound:	PF-00695838
Compound Name:	Fesoterodine
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[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	28-Jan-2015	Not applicable (N/A)

ABBREVIATIONS

This is a list of abbreviations that may or may not be used in the protocol.	
Abbreviation	**Term**
5-HMT	5-hydroxymethyltolterodine
Abs	Absolute
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BIC	beads-in-capsule
BUN	blood urea nitrogen
CBCL	Child Behavior Checklist
CDS	core data sheet
CIC	clean intermittent catheterization
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement
DMC	data monitoring committee
EC	ethics committee
EBC	expected bladder capacity
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
GCP	Good Clinical Practice
GPT	Grooved Pegboard Test
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IDC	involuntary detrusor contractions
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
LDH	lactate dehydrogenase
LFT	liver function test
LSLV	last subject last visit
N/A	not applicable
NDO	neurogenic detrusor overactivity
OAB	overactive bladder
PCD	primary completion date

PK	pharmacokinetics
PR	prolonged release
PT	prothrombin time
PVR	post-void residual volume
SAE	serious adverse event
SRSD	single reference safety document
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
UUT	upper urinary tract
VUR	vesicoureteral reflux
XL	extended release

PROTOCOL SUMMARY

Mechanism of Action/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.

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).[1] 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 upper urinary tract (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)[2] 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.

Study Objectives

- **Primary Objective:**
  - To investigate the safety and tolerability of fesoterodine following once daily long-term treatment in Japanese pediatric NDO subjects.
- **Secondary Objective:**
  - To investigate the efficacy of fesoterodine following once daily long-term treatment in Japanese pediatric NDO subjects.

Study Endpoints

- **Efficacy Endpoints**
  - Maximum cystometric bladder capacity defined as maximal tolerable cystometric capacity or until voiding/leaking begins or at 40 cm H_2O.
  - 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 hours.
  - Mean number of incontinence episodes/24 hours.
  - Mean urgency episodes/24 hours if applicable (only for sensate subjects).
  - Mean volume voided per micturition or mean volume per catheterization.
- **Safety Endpoints**
  - Adverse events, including monitoring of targeted events including, but not limited to:
    - Serious adverse event.
    - Anticholinergic effects such as dry mouth, dry eyes and constipation.
    - Central nervous system (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 Checklist (CBCL) and Grooved Pegboard Test (GPT).
- Vital Signs, including heart rate in the context of age-appropriate norms.
- Urinary tract infection (UTI), 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 clean intermittent catheterization (CIC), or with >1 UTI during the study.

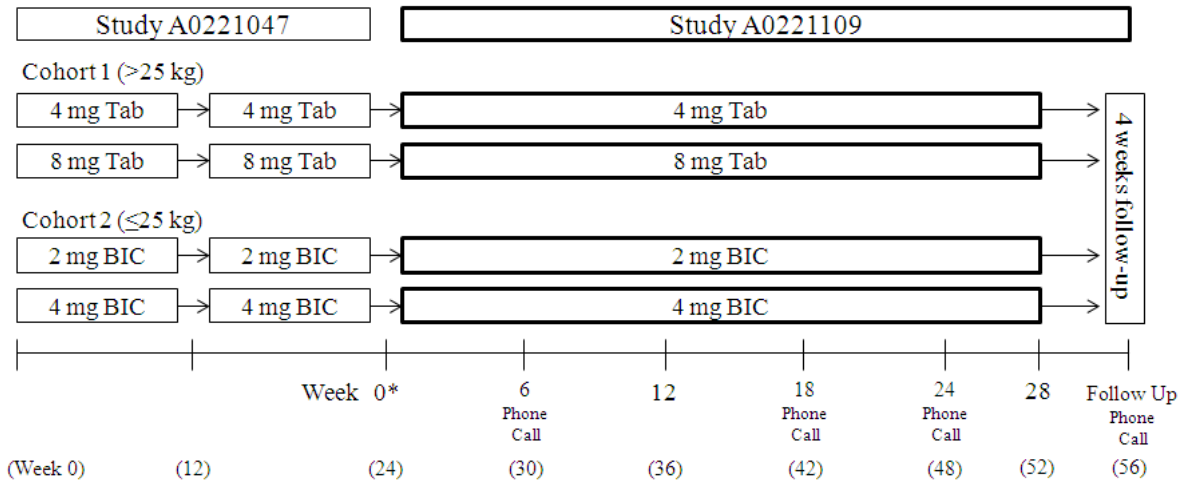
Study Design

This is a Phase 3, multi-center, open-label long-term extension study in Japanese NDO subjects who participated and completed in the precedent Study A0221047 which is a 24 weeks, randomized, open label study, to investigate the safety and tolerability of fesoterodine.

This study consists of a 28-week open-label treatment period followed by a 4-week follow-up. In addition, subjects in the oxybutynin arm of the precedent Study A0221047 will continue the fesoterodine treatment until Week 40 visit in this study, in order to obtain fesoterodine 1 year treatment data.

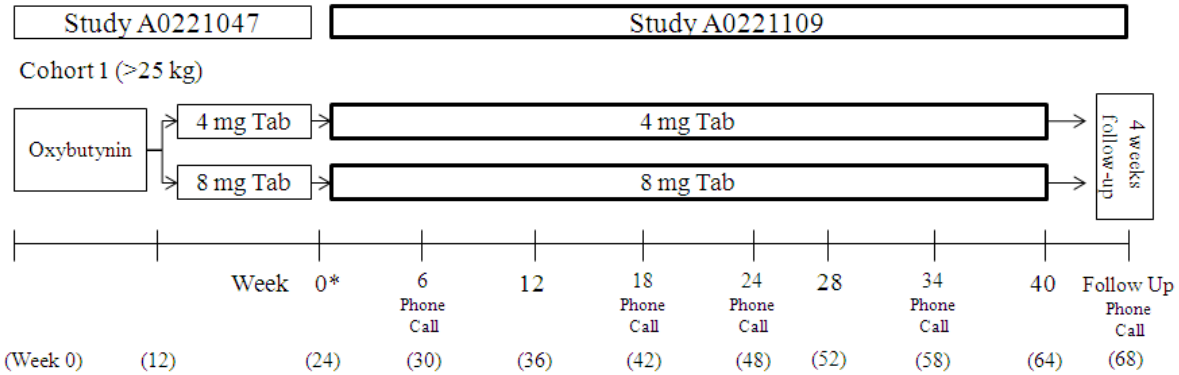
Target number of subjects is not determined because this is the safety extension study but approximately 9 subjects are expected to become eligible for the study.

<u>Subjects who were randomized to Fesoterodine arms in Study A0221047</u>



( ) weeks from baseline of Study A0221047
* Week 0 visit is the same visit as Week 24 visit of Study A0221047.

Subjects who were randomized to Oxybutynin arm in Study A0221047



( ) weeks from baseline of Study A0221047
* Week 0 visit is the same visit as Week 24 visit of Study A0221047.

As a rule, all subjects should continue to receive the allocated dose in Study A0221047 until the end of the trial, unless a safety/toleration problem occurs. But, only if the investigator judges that the continued treatment with low dose (4 mg/day for subjects >25 kg or 2 mg/day for subjects ≤25 kg) is useful to the subject although the high dose (8 mg/day for subjects >25 kg or 4 mg/day for subjects ≤25 kg) is likely to cause some problems with tolerability, and the subject wants the treatment with the low dose, the dosage may be reduced to the low dose at each clinic visits. Dose should not be increased to the high dose.

Subjects >25 kg who cannot swallow tablets are not permitted to take the beads-in-capsule (BIC) formulation and are excluded from the study.

Even if the body weight of subjects with ≤25 kg at baseline of the precedent Study A0221047 increase >25 kg during Study A0221047 or this study, they should maintain the same dose and formulation.

Sample Size Determination

No target number of subjects is determined.

This is an extension study for the subjects who completed Study A0221047 in Japan, and the primary objective is to investigate the safety and tolerability of fesoterodine for these subjects. No statistical testing will be planned but descriptive statistics will be used along with subject narratives. Therefore, the number of subjects to be enrolled in this study is not based on any formal sample size calculation.

In Study A0221047, a few Japanese subjects in cohort 1 (body weight >25 kg) and 9 Japanese subjects in cohort 2 (body weight ≤25 kg) are planned to be enrolled as potential candidate subjects for this study. Assuming a 12.5% drop-out rate in Study A0221047, out of Japanese subjects who are enrolled to Study A0221047, approximately 9 subjects are expected to be enrolled in this study.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Subjects who were randomized to Fesoterodine arms in Study A0221047

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Final Visit [b]	Follow-Up Visit [l]
Week (Weeks from baseline of the precedent Study A0221047)	Week 0 (24)	Week 6 (30)	Week 12 (36)	Week 18 (42)	Week 24 (48)	Week 28 (52)	Week 32 (56)
Allowance (weeks)	-	±2	±2	±2	±2	±2	+2
Clinic visit/Phone call	Clinic visit	Phone call [c]	Clinic visit	Phone call [c]	Phone call [c]	Clinic visit	Phone call [c]
Informed Consent & Assent	X						
Demography	X						
Review Concomitant Medications	X [a]	X	X	X	X	X	X
Adverse Event Monitoring	X [a]	X	X	X	X	X	X
Child Behavior Checklist	X [a]		X			X	
Grooved Pegboard Test	X [a]		X			X	
Vital Signs [d]	X [a]		X			X	
Weight	X [a]		X			X	
Physical Examination [d]	X [a]		X			X	
Visual acuity and accommodation	X [a]		X			X	
Post-void residual volume (PVR) [e]	X [a]		X			X	
Laboratory [f]							
Hematology	X [a]		X			X	
Blood Chemistry	X [a]		X			X	
Urinalysis [g]	X [a]		X			X	
Urine Pregnancy Test [h]	X [a]		X			X	
Urodynamic Studies						X	
Bladder diary [i]						X	
Dosing log [j]	X [a]	X	X	X	X	X [k]	
Study Medication Dispensed	X		X				
Study Medication return/count	X [a]		X			X	
Assess Study Medication compliance	X [a]		X			X	

a. The Week 0 visit of Study A0221109 is the same visit as Week 24 visit of Study A0221047. All procedures done at Week 24 visit of Study A0221047 will be used as the Week 0 data for Study A0221109. These procedures (Study A0221047 procedures) will not be repeated at Week 0 of Study A0221109.

b. Or in the event of the subject withdrawing early from the study. Urodynamic assessment should only be performed in subjects who have not missed any doses in the 3 days prior to the visit.

c. Telephone calls may be substituted by a clinic visit at the discretion of the investigator.

d. If vital signs or physical examinations show a clinically relevant change from baseline of the precedent Study A0221047, 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. Only for female subjects of child-bearing potential. Pregnancy tests may also be repeated as per request of Institutional Review Board (IRB)/Ethics Committee (EC) or if required by local regulations.

i. The bladder diary will be completed for 3 days prior to Final Visit.

j. The dosing log will be completed on a daily basis.

k. At Final Visit, the time of last dose should be recorded.

l. Follow up visit will be done at 4 weeks after Final Visit.

Table 2. Subjects who were randomized to Oxybutynin arm in Study A0221047

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Final Visit [b]	Follow-Up Visit [l]
Week (Weeks from baseline of the precedent Study A0221047)	Week 0 (24)	Week 6 (30)	Week 12 (36)	Week 18 (42)	Week 24 (48)	Week 28 (52)	Week 34 (58)	Week 40 (64)	Week 44 (68)
Allowance (weeks)	-	±2	±2	±2	±2	±2	±2	±2	+2
Clinic visit/Phone call	Clinic visit	Phone call [c]	Clinic visit	Phone call [c]	Phone call [c]	Clinic visit	Phone call [c]	Clinic visit	Phone call [c]
Informed Consent & Assent	X								
Demography	X								
Review Concomitant Medications	X [a]	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X [a]	X	X	X	X	X	X	X	X
Child Behavior Checklist	X [a]		X			X		X	
Grooved Pegboard Test	X [a]		X			X		X	
Vital Signs [d]	X [a]		X			X		X	
Weight	X [a]		X			X		X	
Physical Examination [d]	X [a]		X			X		X	
Visual acuity and accommodation	X [a]		X			X		X	
Post-void residual volume (PVR) [e]	X [a]		X			X		X	
Laboratory [f]									
Hematology	X [a]		X			X		X	
Blood Chemistry	X [a]		X			X		X	
Urinalysis [g]	X [a]		X			X		X	
Urine Pregnancy Test [h]	X [a]		X			X		X	
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Dosing log [j]	X [a]	X	X	X	X	X	X	X [k]	
Study Medication Dispensed	X		X			X			
Study Medication return/count	X [a]		X			X		X	
Assess Study Medication compliance	X [a]		X			X		X	

a. The Week 0 visit of Study A0221109 is the same visit as Week 24 visit of Study A0221047. All procedures done at Week 24 visit of Study A0221047 will be used as the Week 0 data for Study A0221109. These procedures (Study A0221047 procedures) will not be repeated at Week 0 of Study A0221109.
b. Or in the event of the subject withdrawing early from the study. Urodynamic assessment should only be performed in subjects who have not missed any doses in the 3 days prior to the visit.
c. Telephone calls may be substituted by a clinic visit at the discretion of the investigator.
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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).
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1. INTRODUCTION

1.1. Mechanism of Action/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).[3] 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).[4]

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).[5]

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);[2] (Aslan & Kogan, 2002).[4] In children with myelodysplasia, the risk of UUT deterioration and renal damage approaches 80% when no intervention is instituted (Bauer et al, 2002). [3]

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);[2] (Aslan & Kogan, 2002).[4]

Treatment of NDO in children depends on presentation, underlying cause, and the risk of deterioration in function of both upper and lower urinary tract. CIC is first line therapy for bladder emptying in children with areflexic bladders and high PVR, and may be combined with antimuscarinic therapy in specific populations, eg, patients with high pressure bladders as below (Aslan & Kogan, 2002);[4] (Kennelly & DeVoe, 2008).[1]

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).[1] 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)[2] 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 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 OAB in adults; it is not approved for use in the pediatric population.

Fesoterodine functions as a prodrug of 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 and NDO 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 mg and 8 mg once-daily doses to pediatric patients of ages 8-17 years 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 (SAE) 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 objective of this study is to investigate the safety and tolerability of fesoterodine PR tablet 4 mg and 8 mg once daily for 1 year in pediatric NDO subjects aged between 6-17 years with a body weight >25 kg, and fesoterodine BIC 2 mg and 4 mg in subjects ≤25 kg.

Dose Selection Rationale

Study A0221109 is an extension to the 24 weeks randomized, open-label, Phase 3 study (Study A0221047) to provide subjects long-term open-label therapy, thus the doses included in this study are supported by the dose selection rationale for Study A0221047.

Single Reference Safety Document

Complete information for fesoterodine may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To investigate the safety and tolerability of fesoterodine following once daily long-term treatment in Japanese pediatric NDO subjects.

2.1.2. Secondary Objective

- To investigate the efficacy of fesoterodine following once daily long-term treatment in Japanese pediatric NDO subjects.

2.2. Endpoints

2.2.1. Efficacy Endpoints

- Maximum cystometric bladder capacity defined as maximal tolerable cystometric capacity or until voiding/leaking begins or at 40 cm H_2O.
- Detrusor pressure at maximum bladder capacity.
- Presence of IDC.
- Bladder volume at first IDC.
- Bladder compliance.
- Mean number of micturitions and/or catheterizations/24 hours.
- Mean number of incontinence episodes/24 hours.
- Mean urgency episodes/24 hours if applicable (only for sensate subjects).
- Mean volume voided per micturition and/or mean volume per catheterization.

2.2.2. Safety Endpoints

- Adverse events, including monitoring of targeted events including, but not limited to:
    - Serious adverse event.
    - Anticholinergic effects such as dry mouth, dry eyes and constipation.
    - CNS effects such as behavioral changes (eg, aggression), decreased cognitive function, headache, seizures and somnolence.
    - Visual effects such as accommodation disorder, blurred vision, and amblyopia.
- Visual acuity and accommodation tests.
- Cognitive function by the CBCL and GPT.
- Vital Signs, including heart rate in the context of age-appropriate norms.
- UTI, 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.
- PVR in subjects not performing CIC, or with >1 UTI during the study.

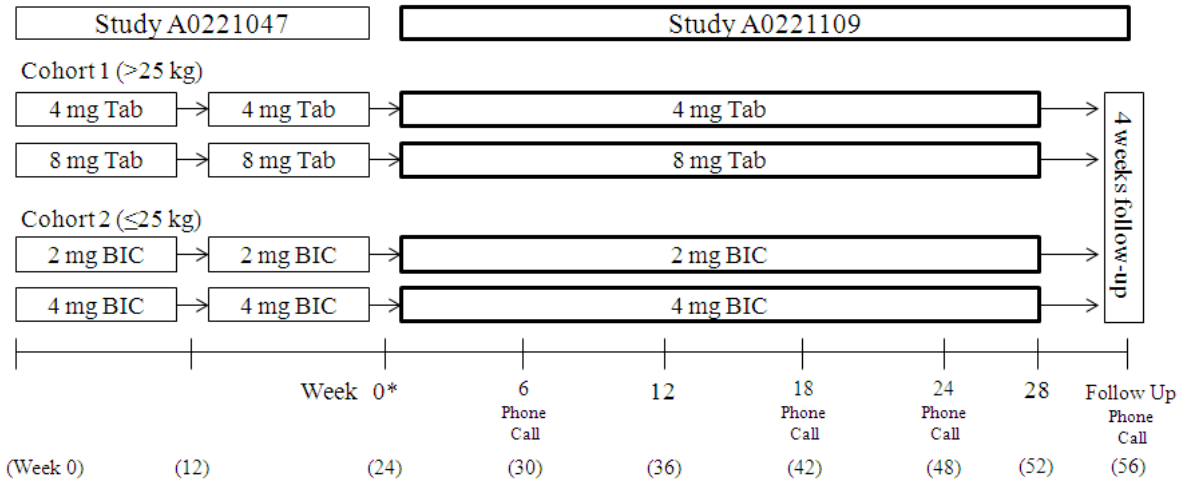
3. STUDY DESIGN

This is a Phase 3, multi-center, open-label long-term extension study in Japanese NDO subjects who participated and completed in the precedent Study A0221047 which is a 24 weeks, randomized, open label study, to investigate the safety and tolerability of fesoterodine.

This study consists of a 28-week open-label treatment period followed by a 4-week follow-up. In addition, subject in the oxybutynin arm of the precedent Study A0221047 will continue the fesoterodine treatment until Week 40 visit in this study, in order to obtain fesoterodine 1 year treatment data (Figure 1 and Figure 2).

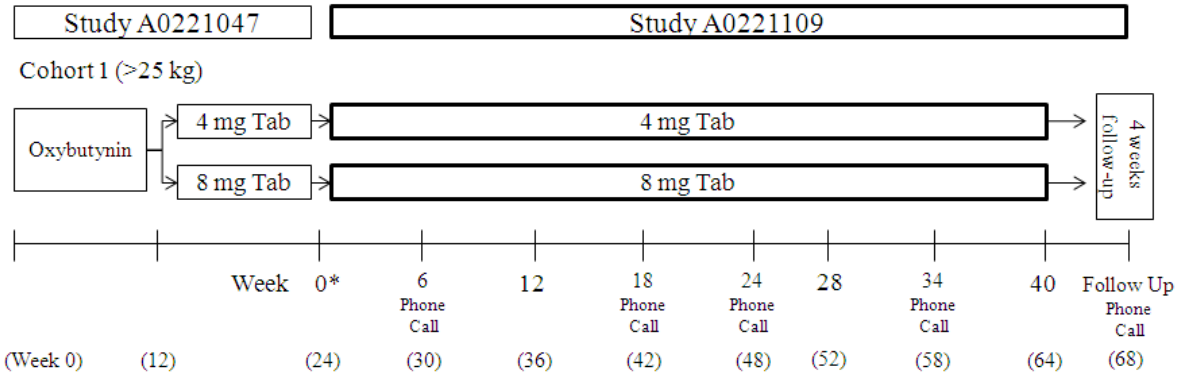
Target number of subjects is not determined because this is the safety extension study but approximately 9 subjects are expected to become eligible for the study.

Figure 1. Study Design (Subjects who were randomized to Fesoterodine arms in Study A0221047)



( ) weeks from baseline of Study A0221047
* Week 0 visit is the same visit as Week 24 visit of Study A0221047.

Figure 2. Study Design (Subjects who were randomized to Oxybutynin arm in Study A0221047)



( ) weeks from baseline of Study A0221047
* Week 0 visit is the same visit as Week 24 visit of Study A0221047.

As a rule, all subjects should continue to receive the allocated dose in Study A0221047 until the end of the trial, unless a safety/toleration problem occurs. But, only if the investigator judges that the continued treatment with low dose (4 mg/day for subjects >25 kg or 2 mg/day for subjects ≤25 kg) is useful to the subject although the high dose (8 mg/day for subjects >25 kg or 4 mg/day for subjects ≤25 kg) is likely to cause some problems with tolerability, and the subject wants the treatment with the low dose, the dosage may be reduced to the low dose at each clinic visits. Dose should not be increased to the high dose.

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

Even if the body weight of subjects with ≤25 kg at baseline of the precedent Study A0221047 increase >25 kg during Study A0221047 or this study, they should maintain the same dose and formulation.

3.1. Study Visits

There will be the following clinic visits:

<u>Subjects who were randomized to Fesoterodine arms in active comparator/efficacy phase in Study A0221047</u>

- Visit 1 (Week 0 [Week 24 in Study A0221047])
- Visit 3 (Week 12)
- Final Visit (Week 28)

<u>Subjects who were randomized to Oxybutynin arms in active comparator phase in Study A0221047</u>

- Visit 1 (Week 0 [Week 24 in Study A0221047])

- Visit 3 (Week 12)
- Visit 6 (Week 28)
- Final Visit (Week 40)

The Week 0 visit of Study A0221109 is the same visit as Week 24 visit of the precedent Study A0221047. All procedures done at Week 24 visit of Study A0221047 will be used as the Week 0 data for Study A0221109.

There will also be a minimum of 3 or 4 telephone calls (or clinic visits) to subjects to identify any new adverse events, review concomitant medication usage and the dosing log at the following telephone calls (or clinic visits).

Subjects who were randomized to Fesoterodine arms in active comparator/efficacy phase in Study A0221047

- Visit 2 (Week 6)
- Visit 4 (Week 18)
- Visit 5 (Week 24)

Subjects who were randomized to Oxybutynin arms in active comparator phase in Study A0221047

- Visit 2 (Week 6)
- Visit 4 (Week 18)
- Visit 5 (Week 24)
- Visit 7 (Week 34)

And there will be a further telephone call (or clinic visit) at:

- Follow-up Visit. To review ongoing or new adverse events, review concomitant medications for subjects 4 weeks after Final Visit. It will also be completed for all subjects who withdraw early from the study and take at least 1 dose of study medication in the A0221109 study.

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 daily dosing log, if needed.

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 nonmedical 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 appropriate 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. Subjects who completed 24 week treatment and all visit procedures in the precedent Study A0221047, and who met the following criteria;

    a. No findings suggestive of worsening condition of NDO compared to baseline of the precedent Study A0221047.

    b. Tolerated the dose of fesoterodine.
    Subjects who did not tolerate the higher dose of fesoterodine (8 mg/day for subjects >25 kg or 4 mg/day for subjects ≤25 kg) well but were not withdrawn can be included; for the A0221109 study the dose can be reduced to low dose of the same formulation (4 mg/day tablet for subjects >25 kg or 2 mg/day BIC for subjects ≤25 kg) (See Section 3).

2. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative/parent(s)/legal guardian) 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.

3. 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 confirmed negative pregnancy tests during Study A0221047.

    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 4.3.

4. 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.

5. 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:

1. Subjects who had major protocol violation (as determined by the Sponsor) in Study A0221047.

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

3. Subjects required to take or expected to initiate concomitant medications during this study that can interact with the PK and/or pharmacodynamics of fesoterodine, such as:

   - Potent CYP3A4 inhibitors.

   - Medications capable of inducing CYP3A4 enzyme metabolism.

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

   - Treatment with botulinum-toxin A.

   - Drugs with antispasmodic, parasympathetic, or cholinergic effects. Stable use of desmopressin for enuresis is allowed if established for at least 3 months prior to the precedent Study A0221047 and during Study A0221047.

4. Intermittent or unstable use of diuretics or alpha blockers, tricyclic antidepressants or any other treatment that may confound the results of the study during the course of the study. Stable usage/dosage is allowed if established for at least 3 months prior to the precedent Study A0221047 and during Study A0221047.

5. Electrostimulation therapy or bladder retraining if started during the precedent Study A0221047 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.

6. Subjects not requiring intermittent catheterization who have a PVR greater than 20 mL as determined by transabdominal ultrasound (eg, bladder scan) immediately after urination. Subjects found to have an elevated PVR >20 mL at Visit 1 (Week 0 [Week 24 in Study A0221047]) will be excluded from the study.

7. Participation in other studies involving investigational drug(s) (Phases 1-4) during study participation.

8. 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.

9. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

10. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

4.3. 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.

4.4. Sponsor's Qualified Medical Personnel

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

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, subject study numbers, 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 subject's 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 the 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, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This is an open label study. As a rule, all subjects should continue to receive the allocated dose in Study A0221047 until the end of the trial, unless a safety/toleration problem occurs. But, only if the investigator judges that the continued treatment with low dose (4 mg/day for subjects >25 kg or 2 mg/day for subjects ≤25 kg) is useful to the subject although the high dose (8 mg/day for subjects >25 kg or 4 mg/day for subjects ≤25 kg) is likely to cause some problems with tolerability, and the subject wants the treatment with the low dose, the dosage may be reduced to the low dose at each clinic visits. Dose should not be increased to the high dose.

5.2. Subject 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:

$$\frac{\textit{Total number of tablets/capsules used since the last clinic visit}}{\textit{Total number of tablets}/\text{capsules}\ \textit{supposed to be taken since the last clinic visit}} \times 100$$

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 each clinic visit (Week 12, Week 28, Week 40 [only for subjects who were randomized to Oxybutynin arm in Study A0221047], 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 one day prior to urodynamic evaluation at Final Visit.

5.3. Drug Supplies

5.3.1. Dosage Form(s) and Packaging

For subjects who was assigned to Cohort 1 (subjects >25 kg) in the precedent Study A0221047, fesoterodine PR 4 mg and 8 mg will be provided by Pfizer as tablets. 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.

For subjects who was assigned to Cohort 2 (subjects ≤25 kg) in the precedent Study A0221047, fesoterodine 2 mg and 4 mg once daily will be provided by Pfizer as a BIC formulation. 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 each clinic visit except for Final Visit, subjects will be provided study medication.

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

5.3.2. Preparation and Dispensing

Pfizer will provide sufficient amounts of the fesoterodine 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.

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 contract research organization (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. Administration

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

Subjects who were assigned to Cohort 1 (subjects >25 kg) in the precedent Study A0221047

Subjects will be instructed to take study medication according to this protocol.

For fesoterodine 4 mg and 8 mg, subjects will swallow one tablet each day without chewing.

Subjects who were assigned to Cohort 2 (subjects ≤25 kg) in the precedent Study A0221047

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).

All Subjects

Subjects will also be asked to complete a daily dosing log (Section 7.2.10). 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.

5.5. Drug Storage

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational products is stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label.

The BIC product (2 mg and 4 mg) should be stored at 2-8°C. Fesoterodine PR tablets should be stored at room temperature (1-30°C).

Storage conditions stated in the SRSD, which for this study is the IB, will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the storage requirements for take home medications including how to report temperature excursions.

5.6. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

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 each clinic visit, subjects must return all unused study medication and packaging (eg, bottles) to the investigator or an approved representative (eg, pharmacist).

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

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.

5.7. Concomitant Treatment(s)

Concomitant medication information will be collected for all subjects during the study. Information collected must include medication, total daily dose, start date, stop date (if applicable), and primary reason for use.

5.7.1. 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 before and during the precedent Study A0221047.
- Stable use of desmopressin for enuresis is allowed if established for at least 3 months before and during the precedent Study A0221047.
- Subjects who are on an established regimen of electrostimulation therapy or bladder retraining (for at least 30 days prior to screening in the precedent Study A0221047) may remain on this for the duration of the study.

5.7.2. Prohibited Concomitant Therapies

The following concomitant therapies are not permitted:

- Potent CYP3A4 inhibitors (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, mirabegron and trospium).
- Treatment with botulinum-toxin A.
- 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 during the course of the study.
- Electrostimulation therapy or bladder retraining if started during the precedent Study A0221047 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.

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. Subjects who were randomized to Fesoterodine arms in Study A0221047

6.1.1. Visit 1 (Week 0)

Visit 1 (Week 0) is the same visit as Week 24 visit of Study A0221047. All procedures done at Week 24 visit of Study A0221047 will be used as the Visit 1 (Week 0) data for Study A0221109. The Study A0221047 procedures will not be repeated at Week 0 of Study A0221109. The following assessments will be performed:

- Informed consent and subject assent prior to the following assessments at Visit 1 (Week 0).
- Subject demographic details.
- Evaluation of subject's eligibility based on inclusion and exclusion criteria.
- Dispense study medication.

6.1.2. Visit 2 (Week 6, ±14 days)

The following assessments will be performed at Visit 2 (Week 6) by telephone or clinic visit:

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

6.1.3. Visit 3 (Week 12, ±14 days)

The following assessments will be performed at Visit 3 (Week 12):

- Concomitant medication review.
- Review of adverse events.
- CBCL (see Appendix 3).
- GPT.
- Vital signs measurement (blood pressure, heart rate, temperature) after the subject has been in a sitting/resting position for at least 5 minutes.
- Physical examination and weight measurement.
- Visual acuity and accommodation assessment.

- In subjects who are not performing intermittent catheterization, perform PVR assessment using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. Assessment of PVR in subjects performing CIC should also be carried out in the event that they experience >1 UTI during the study A0221047 and this study. PVR assessment is not required in subjects who empty their bladder using intermittent catheterization unless otherwise indicated (Section 7.2.5).

- Clinical laboratory testing (approximately 5.5 mL of blood; see Appendix 2) including:

  - Hematology.

  - Blood chemistry.

  - Urinalysis and urine microscopy, culture and sensitivity if indicated.

  - Urine pregnancy test for all female subjects of childbearing potential.

- Review dosing log.

- Dispense study medication.

- Study medication return/count; assess compliance with study medication regimen.

6.1.4. Visit 4 and 5 (Week 18 and 24, ±14 days)

The same assessments as on Visit 2 (Week 6) will be performed at Visit 4 and 5 (Week 18 and 24) by telephone or clinic visit.

6.1.5. Final Visit (Week 28, ±14 days) or Early Withdrawal

Final Visit (Week 28) may be performed over 2 separate days if required. The same assessments as on Visit 3 (Week 12) will be performed at Final Visit (Week 28), except for study medication dispensing.

In addition, the following assessments will be performed:

- Review bladder diary for completeness and check subject understanding of completion.

- Perform urodynamic assessment including imaging of UUT if appropriate. Attempts should be made to perform an urodynamic assessment in subjects who withdraw prior to Final Visit and who have not missed any doses in the three days prior to the visit.

- Review dosing log, and record details of time of the last dose of fesoterodine.

6.1.6. Follow-up visit (Week 32 +14 days)

The following assessments will be performed at Follow-up visit (Week 32) 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 4 weeks after stopping study medication.

6.2. Subjects who were randomized to Oxybutynin arm in Study A0221047

6.2.1. Visit 1 (Week 0)

Visit 1 (Week 0) is the same visit as Week 24 visit of Study A0221047. All procedures done at Week 24 visit of Study A0221047 will be used as the Visit 1 (Week 0) data for Study A0221109. The Study A0221047 procedures will not be repeated at Week 0 of Study A0221109. The following assessments will be performed:

- Informed consent and subject assent prior to the following assessments at Visit 1 (Week 0).
- Subject demographic details.
- Evaluation of subject's eligibility based on inclusion and exclusion criteria.
- Dispense study medication.

6.2.2. Visit 2 (Week 6, ±14 days)

The following assessments will be performed at Visit 2 (Week 6) by telephone or clinic visit:

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

6.2.3. Visit 3 (Week 12, ±14 days)

The following assessments will be performed at Visit 3 (Week 12):

- Concomitant medication review.
- Review of adverse events.
- CBCL (see Appendix 3).
- GPT.
- Vital signs measurement (blood pressure, heart rate, temperature) after the subject has been in a sitting/resting position for at least 5 minutes.

- Physical examination and weight measurement.
- Visual acuity and accommodation assessment.
- In subjects who are not performing intermittent catheterization, perform PVR assessment using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. Assessment of PVR in subjects performing CIC should also be carried out in the event that they experience >1 UTI during the study A0221047 and this study. PVR assessment is not required in subjects who empty their bladder using intermittent catheterization unless otherwise indicated (Section 7.2.5).
- Clinical laboratory testing (approximately 5.5 mL of blood; see Appendix 2) including:
  - Hematology.
  - Blood chemistry.
  - Urinalysis and urine microscopy, culture and sensitivity if indicated.
  - Urine pregnancy test for all female subjects of childbearing potential.
- Review dosing log.
- Dispense study medication.
- Study medication return/count; assess compliance with study medication regimen.

6.2.4. Visit 4 and 5 (Week 18 and 24, ±14 days)

The same assessments as on Visit 2 (Week 6) will be performed at Visit 4 and 5 (Week 18 and 24) by telephone or clinic visit.

6.2.5. Visit 6 (Week 28, ±14 days)

The same assessments as on Visit 3 (Week 12) will be performed at Visit 6 (Week 28).

6.2.6. Visit 7 (Week 34, ±14 days)

The same assessments as on Visit 2 (Week 6) will be performed at Visit 7 (Week 34) by telephone or clinic visit.

6.2.7. Final Visit (Week 40, ±14 days) or Early Withdrawal

Final Visit (Week 40) may be performed over 2 separate days if required. The same assessments as on Visit 3 (Week 12) will be performed at Final Visit (Week 40), except for study medication dispensing.

In addition, the following assessments will be performed:

- Review bladder diary for completeness and check subject understanding of completion.

- Perform urodynamic assessment including imaging of UUT if appropriate. Attempts should be made to perform an urodynamic assessment in subjects who withdraw prior to Final Visit and who have not missed any doses in the three days prior to the visit.

- Review dosing log, and record details of time of the last dose of fesoterodine.

6.2.8. Follow-up visit (Week 44 +14 days)

The following assessments will be performed at Follow-up visit (Week 44) 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 4 weeks after stopping study medication.

6.3. Additional Contacts

Other contacts may also be made, as appropriate, 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:

- Approximately 1 week prior to Final visit, to remind the subject to complete the bladder diary and to review instructions on proper completion if needed.

6.4. Subject Withdrawal

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

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. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. 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), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

If a subject withdraws from the study prior to Final visit (Week 28 in subjects who were randomized to Fesoterodine arms in Study A0221047, or Week 40 in subjects who were randomized to Oxybutinin arm in Study A0221047), the same assessments as at Final

visit should be performed if possible. Urodynamic assessment should only be performed in subjects who have not missed any doses in the 3 days prior to the visit.

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 4 weeks after stopping study medication, and have the same assessments performed as at Follow-up visit.

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 it unfeasible to perform the test. 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 that he or she has 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 Final Visit (Neveus, et al, 2006).[5] It should be performed with the subject awake, or if necessary under sedation, but general anesthesia is not permitted under this protocol. 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 (EBC) 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 case report form (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_2O.
- Detrusor pressure at maximum bladder capacity.

- Maximum detrusor pressure.
- Presence of 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, urodynamic assessments for a subject should be performed by the same person in both this study and Study A0221047. 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 an urodynamic assessment in subjects who withdraw prior to Final Visit and who have not missed any doses in the 3 days prior to the visit.

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 Final Visit, using paper diary. 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). [5]

A proxy (eg, parent or teacher) may assist with completion of the diary if necessary. Contact should be made approximately 1 week prior to Final Visit, to remind the subject to complete the bladder diary and to review instructions on proper completion.

7.2. Safety Assessments

7.2.1. Vital Signs

Blood pressure, temperature and pulse rate should be measured at each clinic visit. This schedule of measurements should provide adequate indication of any clinically relevant changes. However, if vital signs show a clinically relevant change from baseline of Study A0221047, 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 as Study A0221047 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) as Study A0221047 will be used throughout the study.

The same size blood pressure cuff as Study A0221047, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure 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 each clinic visit, 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 of the precedent Study A0221047, 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 each clinic visit. 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.

Even if the body weight of subjects with ≤25 kg at baseline of the precedent Study A0221047 increase >25 kg during Study A0221047 or this study, they should maintain the same dose and formulation.

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 each clinic visit.

Amplitude of accommodation will be assessed by the push up test to assess minimum focusing distance at each clinic visit. 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. Post-Void Residual Volume (PVR)

PVR urine volume in subjects not performing CIC will be assessed using trans-abdominal ultrasound (eg, bladder scan) immediately after urination. If at Visit 1 (Week 0 [Week 24 in Study A0221047]), the measured volume is higher than 20 mL (see exclusion criterion 6), 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 A0221047 and this study.

7.2.6. Clinical Laboratory Evaluation

Safety laboratory tests will be performed at each clinic visit, or as needed to follow-up on significant findings.

Table 3. Safety Laboratory

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count with differential as below: Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	GOT (AST) GPT (ALT) GGT Total and direct bilirubin Alkaline phosphatase LDH CPK BUN Creatinine [a] Uric acid Total protein Sodium Potassium Chloride Albumin Corrected calcium Bicarbonate Phosphorus Glucose (non fasting)	Urine will be tested for the following using a urine dipstick: pH Specific gravity Leukocyte esterase Nitrites Glucose Protein Blood Ketones Urine microscopy, culture and sensitivity [b]	Pregnancy Test [c] (urine)

a. 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.

b. 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).

c. 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 Institutional Review Board (IRB)/Ethics Committee (EC) or if required by local regulations.

7.2.7. Childhood Behavior Checklist (CBCL) (Appendix 3)

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 each clinic visit.

7.2.8. Grooved Pegboard Test (GPT)

The GPT 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 each clinic visit.

7.2.9. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed before investigational product administration at Visit 1 (Week 0 [Week 24 in Study A0221047]) and at the end of treatment visit. 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 each study visit to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRB/EC or if required by local regulations.

7.2.10. 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 paper dosing diary. The dosing log should be completed every day. A proxy (eg, parent) may assist with completion of the dosing log if necessary.

The time of the last dose prior to Final Visit 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 nonserious AE 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 study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides 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. SAEs 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 SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.

AEs (serious and nonserious) should be recorded on the CRF from the time the subject has taken at least 1 dose of study treatment through the last subject visit.

8.3. Definition of an Adverse Event

An AE 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 AEs 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 (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

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 medication error CRF which is a specific version of the AE page, 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 should be captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE 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 AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

An SAE 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 AE 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.

8.6.1. 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).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level 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 (baseline of the precedent Study A0221047) 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 values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

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

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X ULN (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 measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (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 person, 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 liver function test (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 SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. 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, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);

- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

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

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. 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 AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE 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 (see section on Reporting Requirements). 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 that an SAE 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 SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

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

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male subject has been exposed (eg, because of 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 a 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 (SAE) Report Form and Exposure During Pregnancy (EDP) 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 EDP supplemental form. This must be done irrespective of whether an AE 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 general information on the pregnancy and its outcome for all EDP 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 EDP supplemental 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 preprocedure 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 reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to 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 Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report form is maintained in the study master file.

8.12. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent/legally acceptable representative. In addition, each study subject/parent/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE 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 or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames 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 SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE 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, vaccines, and/or 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.

8.14.2. Nonserious Adverse Event Reporting Requirements

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

8.14.3. Sponsor Reporting Requirements to Regulatory Authorities

AE 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.

9.1. Sample Size Determination

No target number of subjects is determined.

This is an extension study for the subjects who completed Study A0221047 in Japan and the primary objective is to investigate the safety and tolerability of fesoterodine for these subjects. No statistical testing will be planned but descriptive statistics will be used along

with subject narratives. Therefore, the number of subjects to be enrolled in this study is not based on any formal sample size calculation.

In Study A0221047, a few Japanese subjects in cohort 1 (body weight >25 kg) and 9 Japanese subjects in cohort 2 (body weight ≤25 kg) are planned to be enrolled as potential candidate subjects for this study. Assuming a 12.5% drop-out rate in Study A0221047, out of Japanese subjects who are enrolled to Study A0221047, approximately 9 subjects are expected to be enrolled in this study.

9.2. Efficacy Analysis

9.2.1. Efficacy Analysis Sets

All efficacy analysis will be used the following full analysis set.

9.2.1.1. Full Analysis Set (FAS)

The Full Analysis Set will include all subjects who have been enrolled and received at least one dose of study medication and have at least 1 observation in efficacy endpoint data after baseline visit in this study.

9.2.2. Analysis of Efficacy Endpoints

All Efficacy endpoints will be summarized descriptively for FAS by timepoint from baseline visit of A0221047 to final visit of this study, using: N, mean, standard deviation, median, minimum and maximum. Subgroup analyses will be conducted that exclude oxybutynin treatment group in cohort 1 of A0221047 from FAS for all efficacy endpoints if any subjects who were randomized to oxybutynin group in A0221047 are included in FAS. In addition, summary statistics for each cohort and that for each randomized treatment group by cohorts in study A0221047 will be provided as same manner as the above.

Listing tables will be provided at each timepoint from baseline visit of A0221047 to final visit of this study for all efficacy endpoints with subjects information (i.e., subject ID, gender, age, body weight at baseline of A0221047, cohort of A0221047, randomized treatment group in A0221047 and treatment history from the A0221047 start to the end of this study). Also, a summary narrative of efficacy and safety data in each subject will be provided.

9.2.3. Analysis of Other Endpoints

No other endpoint in this study.

9.3. Safety Analysis

The Safety Analysis Set will be defined as all randomized subjects who have received at least one dose of study medication in this study.

Results from the safety assessments and any AEs will be presented in tabular and/or graphical format adhering to current Pfizer Data Standards. These presentations will be

split by treatment group at baseline in this study. In addition, AE tables during the period from A0221047 study start to end of this study will be produced by cohort and randomized treatment group in A0221047 (including overall summary of safety analysis set in this study). Safety endpoints such as vital signs, laboratory evaluations, weight, PVR, vision testing and CBCL/GPT results will be presented descriptively by treatment group at baseline in this study. Adverse event incidence rates will be provided descriptively.

9.4. Interim Analysis

No interim analysis will be planned in this study.

9.5. Data Monitoring Committee

This study will use an external data monitoring committee (EDMC).

The EDMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. 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 that 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 AEs, vision testing, CBCL/GPT assessments, vital signs including heart rate, incidence of UTI (as evidenced by urinalysis, urine microscopy and culture), clinical laboratory evaluations in the context of age-appropriate norms, with particular reference to LFTs and renal chemistry, and PVR in subjects not performing CIC, or with >1 UTI during the study.

Assessment of AEs 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 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 Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors 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)/ethics committee (EC), 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 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 are true. Any corrections to entries made in the CRFs or 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/assent documents, 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, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to 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 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)/Ethics Committee (EC)

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

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC 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 GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, 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 or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code

consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must be re-consented as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements approved by ECs 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 ECs.

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 that 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

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, 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 studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of 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, Food and Drug Administration (FDA)-approved products, Pfizer posts results within 1 year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results 1 year from 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 1 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 1 year of discontinuation of the program (if there are no plans for outlicensing, or within 2 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 study concluded according to the prespecified protocol or was terminated.

www.pfizer.com

Pfizer posts clinical trial results on www.pfizer.com for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on www.clinicaltrials.gov.

EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The 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, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The 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 multicenter study, the 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, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the 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 CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

16. REFERENCES

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

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

3. 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; 2002:2231-61.

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

5. 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.

Appendix 1. Examples of CYP3A4 Inducers and Potent CYP3A4 Inhibitors

Potent CYP3A4 inhibitors, 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 nevirapine barbiturates carbamazepine glucocorticoids modafinil oxcarbazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort Troglitazone	indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir telithromycin

Appendix 2. Total Volume of Trial-Related Blood Loss

		Volume of whole blood				
Study Arm in Study A0221047		**Fesoterodine arm**		**Oxybutynin arm**		
Test panel	**Test**	**Visit 3 Week 12**	**Final Visit Week 28**	**Visit 3 Week 12**	**Visit 6 Week 28**	**Final Visit Week 40**
Hematology	Hemoglobin Hematocrit RBC count Platelet count WBC count with differential of total neutrophils, eosinophils, monocytes, basophils, lymphocytes	2 mL	2 mL	2 mL	2 mL	2 mL
Chemistry	GOT (AST) GPT (ALT) GGT Total and direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatine phosphokinase (CPK) Blood urea nitrogen (BUN) Creatinine Uric acid Total protein Albumin Sodium Potassium Chloride Bicarbonate Phosphorus Corrected calcium Glucose (non-fasting)	3.5 mL	3.5 mL	3.5 mL	3.5 mL	3.5 mL
Total blood volume	Total volume per visit	5.5 mL	5.5 mL	5.5 mL	5.5 mL	5.5 mL
	Total volume over study	11.0 mL		16.5 mL		

Additional blood samples may be taken as needed to follow-up on significant findings, or as clinically indicated.

	Guidelines[a]	**A0221109 blood loss volume**
Maximum total volume at a single time	20 mL[b]	5.5 mL
Maximum total volume in a 4 week period	60 mL[c]	5.5 mL
Maximum *possible* total volume in a 4 week period (assuming subject withdraws prior to Final Visit, and within 4 weeks of Visit 7 of Study A0221047, or Visit 3 or 6 of Study A0221109)	60 mL	11.0 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

Appendix 3. 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				