CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Fesoterodine

Clinical Study Report Synopsis: Protocol A0221109

Protocol Title: 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

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: This study was conducted at 7 centers in Japan. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 05 June 2015

Study Completion Date: 01 April 2020

Report Date: 13 August 2020

Previous Report Date(s): Not applicable

Phase of Development: Phase 3

Primary and Secondary Study Objectives and Endpoints:

The study objectives and endpoints are summarized in Table S1.

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint

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

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

Abbreviations: CBCL=child behavior checklist; CIC=clean intermittent catheterization; GPT=grooved pegboard test; H_2O=water; IDC=involuntary detrusor contractions; NDO=neurogenic detrusor overactivity; PVR=post-void residual volume; UTI=urinary tract infection.

METHODS

Study Design: This was a Phase 3, multicenter, open-label long-term treatment study in Japanese neurogenic detrusor overactivity (NDO) subjects aged 6 to 17 years old who participated in and completed the precedent Study A0221047 (A 24-week randomized, open-label, study to evaluate the safety and efficacy of fesoterodine in subjects aged

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6 to 17 years with symptoms of detrusor overactivity associated with a neurological condition [neurogenic detrusor overactivity] [NCT01557244]).

This study consisted of a 28-week open-label treatment period followed by a 4-week follow-up for subjects who were treated with 4 mg or 8 mg tablet of fesoterodine in the precedent Study A0221047. However, subjects who were treated with oxybutynin and switched to 4 mg or 8 mg tablet of fesoterodine in the precedent Study A0221047 were to continue treatment with 4 mg or 8 mg fesoterodine tablet until Week 40 in this study, in order to obtain fesoterodine 1 year treatment data. A target number of subjects was not determined because this was the safety extension study but approximately 9 subjects were expected to become eligible for the study.

Diagnosis and Main Criteria for Inclusion: Subjects who completed 24 week treatment and all visit procedures up to Visit 7 (Week 24) in the precedent Study A0221047 with no findings suggestive of worsening condition of NDO compared to baseline of the precedent Study A0221047. Subjects who did not tolerate the higher dose of fesoterodine (8 mg/day for subjects >25 kg or 4 mg/day beads-in-capsule (BIC) for subjects ≤25 kg) well but were not withdrawn could be included; for this study the dose could 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) were included in the study.

Subjects who had major protocol violation (as determined by the sponsor) in Study A0221047, subjects with intermittent or unstable use of diuretics or α blockers, tricyclic antidepressants or any other treatment that could have confound the results of the study during the course of the study, and subjects not requiring intermittent catheterization who had a post-void residual volume (PVR) >20 mL as determined by transabdominal ultrasound (eg, bladder scan) immediately after urination were excluded.

Study Treatment:

This was an open-label study. All subjects continued to receive the dose randomized in Study A0221047.

For subjects who were assigned to Cohort 1 (subjects >25 kg) in the precedent Study A0221047, fesoterodine prolonged release (PR) 4 mg and 8 mg were provided by the sponsor as PR tablets for oral administration. Subjects swallowed 1 tablet each day without chewing.

For subjects who were assigned to Cohort 2 (subjects ≤25 kg) in the precedent Study A0221047, fesoterodine 2 mg and 4 mg once daily were provided by the sponsor as a BIC formulation for oral administration. Subjects took 1 capsule per day without chewing. For subjects who could not swallow whole capsules, the capsule could have been opened and the beads sprinkled on a suitable medium (eg, apple sauce).

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Subjects were provided with the study medication at each clinic visit except for the Final Visit.

Subjects >25 kg who could not swallow tablets were not permitted to take the BIC formulation, and were excluded from the study.

All subjects were also asked to complete a daily dosing log. If information from the dosing log indicated that the subject had not taken study drug in accordance with dosing instructions, the subject and their legal representatives were re-instructed on how to take the investigational product, and followed-up as appropriate by the investigator or approved representative to ensure understanding and compliance.

The description of the investigational product is provided in Table S2.

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Fesoterodine fumarate PR 4 mg light blue oval film coated tablet	15-003448	15-004990	4 mg	Tablet
Fesoterodine fumarate PR 4 mg light blue oval film coated tablet	89162001	13-111228	4 mg	Tablet
Fesoterodine fumarate PR 8 mg blue oval film coated tablet	15-003488	15-004983	8 mg	Tablet
Fesoterodine fumarate PR 8 mg blue oval film coated tablet	89098001	13-111229	8 mg	Tablet
PF-00695838-42 fesoterodine fumarate 2 mg CR capsules SR4	SW-SDM	15-007270	2 mg	Capsule
PF-00695838-42 fesoterodine fumarate 4 mg CR capsules SR4	SW-SDM	15-007271	4 mg	Capsule

Abbreviations: CR=controlled release; PR=prolonged release; SR=sustained release.

Efficacy Evaluations:

Urodynamic Assessments: Urodynamic assessment was performed at Final Visit. The urodynamic assessments included evaluation of following parameters:

- 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 involuntary detrusor contractions (IDC).

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- Bladder volume at first IDC, if present.

- Bladder wall compliance (mL/cm H_2O), defined as Δvolume/Δpressure during that change in bladder volume.

Where possible, urodynamic assessments for a subject were to be performed by the same person in this study who performed in precedent Study A0221047. Only the central reader's assessment of the urodynamic evaluation was recorded.

Bladder Diary: A bladder diary was 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) were recorded.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations: There were no pharmacokinetic (PK), pharmacodynamics (PD), pharmacogenomic, and/or other evaluations done in this study.

Safety Evaluations: Safety assessments consisted of the collection of adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination, weight measurements, visual acuity and accommodation, PVR, clinical laboratory evaluations, Child Behavior Checklist (CBCL), Grooved Pegboard Test (GPT) pregnancy testing and dosing log.

Statistical Methods:

The following analysis sets were used in this study:

Full Analysis Set (FAS): The FAS included all subjects who had been enrolled and received at least 1 dose of investigational product and had at least 1 observation in efficacy endpoint data after baseline visit in Study A0221109.

Safety Analysis Set: The safety analysis set included all subjects who had been enrolled and received at least 1 dose of investigational product in Study A0221109.

Efficacy endpoints and treatment-emergent adverse event (TEAEs) were summarized using merged data of precedent Study A0221047 and Study A0221109. When the longitudinal changes were analyzed for the merged data, baseline was Visit 1 (Screening) or Visit 2 (Day 1) of Study A0221047. Demographics and baseline characteristics including medical history, prior drug/non-drug treatments used baseline information at Visit 1 (Screening) or Visit 2 (Day 1) of Study A0221047. Other safety endpoints were summarized for the data of Study A0221109 alone, and baseline was Week 0 of Study A0221109.

There were no statistical hypotheses in this study. No imputation for missing data was planned for efficacy and safety analyses.

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All efficacy endpoints of continuous data and their change from baseline were summarized descriptively by each visit. The presence of IDC was summarized by each visit.

TEAEs were summarized for the total of treatment groups, each cohort and each treatment group of Study A0221047, using the merged data of Study A0221047 and this study. TEAEs were also summarized by the period of the onset time from the start of the fesoterodine treatment (0 to 12 weeks, 13 to 24 weeks, 25 to 36 weeks, or after 37 weeks).

The incidence of laboratory abnormalities observed at any time during the study was tabulated following Pfizer Data Standard and summary statistics for changes from baseline was provided by each visit.

Blood pressure (BP) and pulse rate and their changes from baseline were summarized descriptively for each treatment group by each visit. PVR, visual acuity and accommodation, CBCL, and GPT and their changes from baseline were summarized descriptively for each label, by each visit.

RESULTS

Subject Disposition and Demography: Of the 12 subjects screened for entry into the study; 2 subjects were assigned to treatment in Cohort 1, and 10 subjects were assigned to treatment in Cohort 2.

In Cohort 1, 2 subjects were assigned to treatment in fesoterodine 8 mg arm. In Cohort 2, 10 subjects were assigned to treatment: 7 subjects to fesoterodine 2 mg BIC arm and 3 subjects to fesoterodine 4 mg BIC arm. There were no subjects who had been initially randomized to oxybutynin arm in Study A0221047 and participated in this study.

Eleven subjects (91.7%) completed the study. One subject in Cohort 2 in the fesoterodine 2 mg BIC arm discontinued the study due to withdrawal by parent/guardian (the subject and parent/guardian decided to withdraw from this study at their own will due to surgery for ventriculo-peritoneal shunt reconstruction). All subjects were analyzed for efficacy and safety.

The subject evaluation by treatment groups at baseline is presented in Table S3.

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Table S3. Subject Evaluation Groups by Treatment Groups at Baseline in A0221109

	Cohort 1 (N=2)	Cohort 2 (N=10)	Fesoterodine 4 mg Tab (A0221109) (N=0)	Fesoterodine 8 mg Tab (A0221109) (N=2)	Fesoterodine 2 mg BIC (A0221109) (N=7)	Fesoterodine 4 mg BIC (A0221109) (N=3)	Total (N=12)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Screened: 12							
Assigned to Treatment	2 (100.0)	10 (100.0)	0	2 (100.0)	7 (100.0)	3 (100.0)	12 (100.0)
Treated	2 (100.0)	10 (100.0)	0	2 (100.0)	7 (100.0)	3 (100.0)	12 (100.0)
Completed	2 (100.0)	9 (90.0)	0	2 (100.0)	6 (85.7)	3 (100.0)	11 (91.7)
Discontinued	0	1 (10.0)	0	0	1 (14.3)	0	1 (8.3)
Analysis for Efficacy:							
Full Analysis Set	2 (100.0)	10 (100.0)	0	2 (100.0)	7 (100.0)	3 (100.0)	12 (100.0)
Analysis for Safety:							
Safety Analysis Set	2 (100.0)	10 (100.0)	0	2 (100.0)	7 (100.0)	3 (100.0)	12 (100.0)
CCI [redacted]							

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In Cohort 1, fesoterodine 8 mg arm, both the subjects were female. Additionally, both the subjects were Asian with a mean weight of 51.7 kg, and the mean age was 13.5 years.

In Cohort 2, 9 subjects were male and 1 subject was female. In the fesoterodine 2 mg BIC arm all the subjects were male (n=7) while in the fesoterodine 4 mg BIC arm, 2 subjects were male and 1 subject was female. Additionally, all the subjects were Asian with a mean weight of the subjects was 18.99 kg and 20.77 kg in the fesoterodine 2 mg and 4 mg BIC arms, respectively. The mean age of the subjects was 7.9 years and 7.3 years in the fesoterodine 2 mg and 4 mg BIC arms, respectively.

Efficacy Results:

Maximum Cystometric Bladder Capacity:

The maximum cystometric bladder capacity (MCBC) was increased in subjects treated with fesoterodine at Week 12; a numerical increase was consistent with the results seen across both cohorts for Study A0221047. The numerical increase was also observed at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine. The mean (standard deviation [SD]) change from baseline in MCBC in total fesoterodine treated subjects was 61.3 mL (53.98) and 53.1 mL (59.74) at Week 12 and Week 52, respectively.

Detrusor Pressure at Maximum Bladder Capacity:

Detrusor pressure at maximum bladder capacity was decreased in subjects treated with fesoterodine at Week 12; a numerical decrease was consistent with the results seen across both cohorts for Study A0221047. The numerical decrease was also observed at Week 52 (Week 28 in the current study). The mean (SD) change from baseline in detrusor pressure at maximum bladder capacity in total fesoterodine treated subjects was -12.3 cm H_2O (22.74) and -4.8 cm H_2O (21.43) at Week 12 and Week 52, respectively.

Presence of Involuntary Detrusor Contractions:

Out of 12 subjects treated with fesoterodine, 11 subjects (91.7%) had IDC at baseline. Of these 11 subjects with IDC, 2 subjects (18.2%) showed improvement at Week 52. Other subjects had no change in IDC from baseline at Week 52.

Bladder Volume at First Involuntary Detrusor Contractions:

The bladder volume at first IDC was increased in subjects treated with fesoterodine at Week 12; a numerical increase was consistent with the results seen across both cohorts for Study A0221047. The numerical increase was also observed at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine. The mean (SD) change from baseline in bladder volume at first IDC in total fesoterodine treated subjects was 95.0 mL (53.88) and 50.4 mL (36.38) at Week 12 and Week 52, respectively.

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Bladder Compliance:

The bladder compliance was increased in subjects treated with fesoterodine at Week 12; a numerical increase was consistent with the results seen across both cohorts for Study A0221047. The numerical increase was also observed at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine. The mean (SD) summary of change from baseline in bladder compliance in total fesoterodine treated subjects was 18.22 mL/cm H_2O (42.021) and 12.39 mL/cm H_2O (15.194) at Week 12 and Week 52 (Week 28 in the current study), respectively.

Mean Number of Micturitions or Catheterizations per 24 Hours:

The mean (SD) change from baseline in mean number of micturitions or catheterizations per 24 hours was -0.46 (1.055) at Week 12 and -0.41 (0.758) at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

Mean Number of Micturitions per 24 Hours: The mean (SD) change from baseline in mean number of micturitions per 24 hours was -1.50 (1.036) at Week 12 and -1.08 (0.631) at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

Mean Number of Catheterizations per 24 Hours: The mean (SD) change from baseline in mean number of catheterizations per 24 hours was 0.04 (0.353) at Week 12 and -0.02 (0.302) at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

Mean Number of Incontinence Episodes per 24 Hours:

The mean (SD) change from baseline in mean number of incontinence episodes per 24 hours was -0.07 (1.586) at Week 12 and 0.08 (1.615) at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

Mean Urgency Episodes per 24 Hours (Only for Sensate Subjects):

The mean (SD) change from baseline in mean number of urgency episodes per 24 hours was -0.61 (0.347) at Week 12 and Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

Mean Volume Voided per Micturition and/or Mean Volume per Catheterization:

The mean (SD) change from baseline in mean volume voided per micturition or catheterization was 14.75 mL (18.638) at Week 12 and 4.75 mL (29.583) at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

The mean (SD) change from baseline in mean volume voided per micturition was 15.77 mL (6.924) at Week 12 and 4.75 mL (14.496) at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

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The mean (SD) change from baseline in mean volume per catheterization was 17.06 mL (21.739) at Week 12 and 4.12 mL (29.591) at Week 52 (Week 28 in the current study) in subjects treated with fesoterodine.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Results:

There were no PK, PD, pharmacogenomic, and/or other evaluations done in this study.

Safety Results:

Summary of Adverse Events:

For all the subjects treated with fesoterodine, 1 SAE was reported in fesoterodine 2 mg BIC arm. This SAE was not treatment-related. There were no severe TEAEs, and no TEAEs leading to discontinuation from the study or from study drug in this study. There was 1 subject (14.3%) with dose reduction or temporary discontinuation due to TEAEs in the fesoterodine 2 mg BIC arm.

For Cohort 1, the TEAEs were reported for 2 subjects (100.0%) in the fesoterodine 8 mg arm. There were no treatment-related TEAEs in Cohort 1.

For Cohort 2, the TEAEs were reported for 9 subjects (90.0%); 6 subjects (85.7%) in the fesoterodine 2 mg BIC arm and 3 subjects (100.0%) in the fesoterodine 4 mg BIC arm. One subject (14.3%) in fesoterodine 2 mg BIC arm and 1 subject (33.3%) in the fesoterodine 4 mg BIC arm reported treatment-related TEAEs.

All-Causality Adverse Events:

The TEAEs by system organ classes (SOCs) and preferred terms (PTs) by cohorts and randomized treatment groups (all-causalities) for safety analysis set are presented in Table S4.

For all the subjects treated with fesoterodine, the TEAEs (all-causalities) by PTs in ≥2 subjects were nasopharyngitis (7 subjects [58.3%]), asymptomatic bacteriuria (4 subjects [33.3%]), pyrexia (3 subjects [25.0%]), influenza, pharyngitis, diarrhea, myopia, upper respiratory tract inflammation and sinusitis (2 subjects [16.7%] each). All the TEAEs reported in each treatment arm were mild to moderate in severity.

For Cohort 1, the incidence of reported TEAEs by SOC are described below:

In Cohort 1, all the TEAEs reported were mild in severity.

For eye disorders SOC, there was a TEAE of visual acuity reduced reported in 1 subject (50.0%).

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For gastrointestinal disorders SOC, the TEAEs of anal fissure and diarrhea were each reported in 1 subject (50.0%).

For infections and infestations SOC, the TEAEs of bronchitis and nasopharyngitis were each reported in 1 subject (50.0%).

For Cohort 2, the incidence of reported TEAEs by SOC are described below:

In Cohort 2, the majority of the TEAEs reported in the fesoterodine 2 mg and 4 mg BIC arm were mild in severity except abscess limb in 1 subject (10.0%) and urinary tract infection in 1 subject (10.0%), which were moderate in severity.

For eye disorders SOC, the TEAEs of astigmatism, conjunctivitis allergic, and strabismus were each reported in 1 subject (14.3%) in the fesoterodine 2 mg BIC arm. The TEAE of myopia was reported in 2 subjects (66.7%) in the fesoterodine 4 mg BIC arm.

For infections and infestations SOC, the TEAEs of asymptomatic bacteriuria was reported in 3 subjects (42.9%) and 1 subject (33.3%), and nasopharyngitis was reported in 4 subjects (57.1%) and 2 subjects (66.7%) respectively in the fesoterodine 2 mg and 4 mg BIC arms.

For skin and subcutaneous tissue disorders SOC, the TEAEs of decubitus ulcer, eczema and seborrheic dermatitis were each reported in 1 subject (14.3%) in the fesoterodine 2 mg BIC arm. The TEAE of dermal cyst was reported in 1 subject (33.3%) in the fesoterodine 4 mg BIC arm.

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Table S4. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Cohorts and Randomized Treatment Groups (All Causalities) - Safety Analysis Set (Merged Data)

Number of Subjects Evaluable for AEs	Cohort 1 (N=2)	Cohort 2 (N=10)	Fesoterodine 8 mg Tab (N=2)	Fesoterodine 2 mg BIC (N=7)	Fesoterodine 4 mg BIC (N=3)	Total (N=12)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With Any adverse event	2 (100.0)	9 (90.0)	2 (100.0)	6 (85.7)	3 (100.0)	11 (91.7)
EYE DISORDERS	1 (50.0)	4 (40.0)	1 (50.0)	2 (28.6)	2 (66.7)	5 (41.7)
Astigmatism	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Conjunctivitis allergic	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Myopia	0	2 (20.0)	0	0	2 (66.7)	2 (16.7)
Strabismus	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Visual acuity reduced	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
GASTROINTESTINAL DISORDERS	2 (100)	2 (20.0)	2 (100)	2 (28.6)	0	4 (33.3)
Anal fissure	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
Aphthous ulcer	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Diarrhoea	1 (50.0)	1 (10.0)	1 (50.0)	1 (14.3)	0	2 (16.7)
Faeces soft	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (50.0)	2 (20.0)	1 (50.0)	1 (14.3)	1 (33.3)	3 (25.0)
Fatigue	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
Pyrexia	1 (50.0)	2 (20.0)	1 (50.0)	1 (14.3)	1 (33.3)	3 (25.0)
IMMUNE SYSTEM DISORDERS	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Seasonal allergy	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
INFECTIONS AND INFESTATIONS	2 (100)	9 (90.0)	2 (100)	6 (85.7)	3 (100)	11 (91.7)

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Table S4. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Cohorts and Randomized Treatment Groups (All Causalities) - Safety Analysis Set (Merged Data)

Number of Subjects Evaluable for AEs	Cohort 1 (N=2)	Cohort 2 (N=10)	Fesoterodine 8 mg Tab (N=2)	Fesoterodine 2 mg BIC (N=7)	Fesoterodine 4 mg BIC (N=3)	Total (N=12)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Abscess limb	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Asymptomatic bacteriuria	0	4 (40.0)	0	3 (42.9)	1 (33.3)	4 (33.3)
Bronchitis	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
Conjunctivitis bacterial	0	1 (10.0)	0	0	1 (33.3)	1 (8.3)
Impetigo	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Influenza	0	2 (20.0)	0	2 (28.6)	0	2 (16.7)
Nasopharyngitis	1 (50.0)	6 (60.0)	1 (50.0)	4 (57.1)	2 (66.7)	7 (58.3)
Oral herpes	0	1 (10.0)	0	0	1 (33.3)	1 (8.3)
Pharyngitis	0	2 (20.0)	0	1 (14.3)	1 (33.3)	2 (16.7)
Sinusitis	0	2 (20.0)	0	1 (14.3)	1 (33.3)	2 (16.7)
Urinary tract infection	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
Chillblains	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
INVESTIGATIONS	0	1 (10.0)	0	0	1 (33.3)	1 (8.3)
Urodynamics measurement abnormal	0	1 (10.0)	0	0	1 (33.3)	1 (8.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Spinal deformity	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
NERVOUS SYSTEM DISORDERS	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
Headache	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)

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Table S4. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Cohorts and Randomized Treatment Groups (All Causalities) - Safety Analysis Set (Merged Data)

Number of Subjects Evaluable for AEs	Cohort 1 (N=2)	Cohort 2 (N=10)	Fesoterodine 8 mg Tab (N=2)	Fesoterodine 2 mg BIC (N=7)	Fesoterodine 4 mg BIC (N=3)	Total (N=12)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
PRODUCT ISSUES	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Device malfunction	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
RENAL AND URINARY DISORDERS	1 (50.0)	1 (10.0)	1 (50.0)	0	1 (33.3)	2 (16.7)
Renal failure	1 (50.0)	0	1 (50.0)	0	0	1 (8.3)
Urinary incontinence	0	1 (10.0)	0	0	1 (33.3)	1 (8.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	3 (30.0)	0	2 (28.6)	1 (33.3)	3 (25.0)
Asthma	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Upper respiratory tract inflammation	0	2 (20.0)	0	1 (14.3)	1 (33.3)	2 (16.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	4 (40.0)	0	3 (42.9)	1 (33.3)	4 (33.3)
Decubitus ulcer	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Dermal cyst	0	1 (10.0)	0	0	1 (33.3)	1 (8.3)
Eczema	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)
Seborrhoeic dermatitis	0	1 (10.0)	0	1 (14.3)	0	1 (8.3)

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Table S4. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Cohorts and Randomized Treatment Groups (All Causalities) - Safety Analysis Set (Merged Data)

Number of Subjects Evaluable for AEs	Cohort 1 (N=2)	Cohort 2 (N=10)	Fesoterodine 8 mg Tab (N=2)	Fesoterodine 2 mg BIC (N=7)	Fesoterodine 4 mg BIC (N=3)	Total (N=12)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**

Randomized Treatment Groups is based on the randomization information at baseline in A0221047.
Subjects are only counted once per treatment per event.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Includes all data collected since the first dose of study drug.
MedDRA v22.1 coding dictionary applied.
CCI [redacted]

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Treatment-Related Adverse Events:

Three treatment-related TEAEs were observed in 2 subjects treated with fesoterodine. The observed treatment-related TEAEs were diarrhea and faeces soft, each reported in 1 subject (14.3%) in fesoterodine 2 mg BIC arm, and urinary incontinence reported in 1 subject (33.3%) in fesoterodine 4 mg BIC arm.

All the treatment-related TEAEs were mild in severity.

Deaths: There were no deaths reported among subjects who participated in this study.

Serious Adverse Events:

In Cohort 1, no SAEs were reported. In Cohort 2, there was an SAE of urinary tract infection reported for 1 subject (14.3%) in the fesoterodine 2 mg BIC arm. This was an SAE occurred during the precedent Study A0221047.

Discontinuations and Dose Reductions due to Adverse Events:

No subject discontinued from the study due to AEs.

Among the subjects treated with fesoterodine, the TEAEs leading to dose reduction or temporary discontinuation (interruption) of study drug were reported for 1 subject in fesoterodine 2 mg BIC arm. These TEAEs were urinary tract infection (moderate in severity and considered as an SAE), pyrexia and nasopharyngitis (mild in severity). There were no dose reductions or temporary discontinuations due to TEAEs in the fesoterodine 4 mg BIC and fesoterodine 8 mg arms.

There were TEAEs of special interest of visual acuity reduced and headache reported in 1 subject (50.0%) in Cohort 1, fesoterodine 8 mg arm. In Cohort 2, an SAE of special interest of urinary tract infection was reported in 1 subject (14.3%) in the fesoterodine 2 mg BIC arm. There were no TEAEs of special interest in the fesoterodine 4 mg BIC arm.

Clinical Laboratory Evaluations:

In Cohort 1, the laboratory test abnormalities (without regard to baseline abnormality) were reported for 2 subjects (100.0%) in the fesoterodine 8 mg arm. The laboratory test abnormalities were reported as follows:

- Leukocyte esterase ≥1 (1 of 2 subjects [50.0%] in the fesoterodine 8 mg arm);
- Urine leukocytes ≥20/high power field (HPF) (1 of 2 subjects [50.0%] in the fesoterodine 8 mg arm);
- Epithelial cells ≥6/low power field (LPF) (2 of 2 subjects [100.0%] in the fesoterodine 8 mg arm).

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In Cohort 2, the laboratory test abnormalities (without regard to baseline abnormality) were reported for 8 subjects (80.0%) in the fesoterodine 2 mg and 4 mg BIC arm. The most frequently reported laboratory test abnormalities (reported by ≥20% of subjects in either arm) were as follows:

- Eosinophils ($10^3/mm^3$) >1.2 × upper limit of normal (3 of 7 subjects [42.9%] in the fesoterodine 2 mg BIC arm and 1 of 3 subjects [33.3%] in the fesoterodine 4 mg BIC arm);
- Specific gravity (scalar) >1.030 (2 of 7 subjects [28.6%] in the fesoterodine 2 mg BIC arm and 1 of 3 subjects [33.3%] in the fesoterodine 4 mg BIC arm);
- Nitrite ≥1 (2 of 7 subjects [28.6%] in the fesoterodine 2 mg BIC arm and 1 of 3 subjects [33.3%] in the fesoterodine 4 mg BIC arm);
- Leukocyte esterase ≥1 (2 of 7 subjects [28.6%] in the fesoterodine 2 mg BIC arm and 1 of 3 subjects [33.3%] in the fesoterodine 4 mg BIC arm);
- Urine leukocytes ≥20/HPF (1 of 4 subjects [25.0%] in the fesoterodine 2 mg BIC arm);
- Epithelial cells ≥6/LPF (4 subjects [100.0%] in the fesoterodine 2 mg BIC arm and 2 subjects [100.0%] in the fesoterodine 4 mg BIC arm);
- Hyaline casts >1/LPF (1 subject [100.0%] in the fesoterodine 2 mg BIC arm);
- Bacteria >20/HPF (1 of 2 subjects [50.0%] in the fesoterodine 4 mg BIC arm).

There were no apparent trends in median changes from baseline to the last observation in any hematology and clinical chemistry parameters in Cohort 1 and Cohort 2, except for the platelets ($10^3/mm^3$). The total median value at baseline for both the cohorts for platelet ($10^3/mm^3$) was 326, while the total median change from baseline for both the cohorts was 22.

Vital Signs:

For Cohort 1, there were no subjects who met criteria for sitting systolic BP (value of <90 mm Hg), sitting diastolic BP (value of <50 mm Hg) and sitting pulse rate (value of <40 bpm, value of >120 bpm). There were no subjects who met categorical increase or decrease criteria from baseline in sitting systolic/diastolic BP values in Cohort 1.

In Cohort 2, 1 subject (14.3%) had a post-baseline sitting systolic BP value of <90 mm Hg and 2 subjects (28.6%) had sitting diastolic BP value of <50 mm Hg in the fesoterodine 2 mg BIC arm. There were no subjects who met the above categorical criteria for BP in the fesoterodine 4 mg BIC arm. Also, there were no subjects who met the criteria for sitting pulse rate (value of <40 bpm, value of >120 bpm) in Cohort 2.

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One subject (14.3%) met the increase in sitting diastolic BP criterion (change of ≥20 mm Hg increase) in the fesoterodine 2 mg BIC arm. There were no subjects who met this criterion in the fesoterodine 4 mg BIC arm and no subjects meeting the increase in sitting systolic BP criterion (change of ≥30 mm Hg) in either treatment arm. There were no subjects who met categorical decrease from baseline in sitting BP values in Cohort 2.

For Cohort 1 and Cohort 2, no clinically relevant changes from baseline were observed for vital sign parameters.

Physical Findings: There were no clinically significant changes from baseline reported as AEs.

Visual Acuity and Accommodation: For Cohort 1 and Cohort 2, there were no clinically relevant changes from baseline to Week 36 or Week 52 (Week 12 or Week 28 in the current study, respectively) in visual accommodation or visual acuity in either eye.

Cognitive Function:

For Cohort 1 and Cohort 2, there were no clinically relevant changes from baseline to Week 36 or Week 52 (Week 12 or Week 28 in the current study, respectively) in the T score or total score of any CBCL assessments (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, withdrawn, externalizing, internalizing and total problems).

For Cohort 1 and Cohort 2, there were no clinically relevant changes from baseline to Week 36 or Week 52 (Week 12 or Week 28 in the current study, respectively) in GPT results in either the dominant or non-dominant hand.

For the GPT, subjects were assigned to either a 10- or 25-peg assessment based on their age, resulting in small sample sizes for the 25-peg assessment in Cohort 1 and Cohort 2.

Post-Void Residual Volume: In this study, all subjects were performing intermittent catheterization. Therefore, no subjects had a post-void residual urine volume assessment.

Conclusions:

Safety

- Treatment with fesoterodine once daily for 52 weeks was well tolerated in Japanese pediatric NDO subjects with no discontinuations for safety reasons and no treatment-related SAEs.

- No clinically relevant changes were observed for visual acuity and accommodation, cognitive function or behaviour, vital signs values and clinical laboratory tests.

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- No increase in frequency, severity or nature of treatment-related AEs with longer-term exposure was observed in this study, although with limited sample size.

Efficacy

- The sample size of this study was very limited, however, in subjects treated with fesoterodine there was a numerical increase (improvement) in the efficacy endpoint, MCBC, at Week 12, consistent with the A0221047 overall result, and this was also observed at Week 52 (Week 28 in the current study). Numerical improvements from baseline were also observed in other urodynamic endpoints, but this was not consistently observed in the diary-based efficacy endpoints at Week 52.

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