CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Fesoterodine

Clinical Study Report Synopsis: Protocol A0221047

Protocol Title: A 24-Week Randomized, Open-Label, Study to Evaluate the Safety and Efficacy of Fesoterodine in Subjects Aged 6 to 17 Years With Symptoms of Detrusor Overactivity Associated With a Neurological Condition (Neurogenic Detrusor Overactivity)

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

Study Center(s): A total of 65 study sites in Belgium, Canada, Estonia, Finland, France, Germany, Greece, Italy, Japan, Republic of Korea, Lithuania, Malaysia, Philippines, Poland, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, and United States randomized subjects in this study. 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: 02 July 2012 (First Subject First Visit)

Study Completion Date: 13 February 2020 (Last Subject Last Visit)

Report Date: 01 July 2020

Previous Report Date(s): Not applicable

Phase of Development: Phase 3

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Primary and Secondary Study Objectives and Endpoints:

Table S1.   Study Objectives

Type	Objective
Primary	
Safety, Efficacy	To determine the safety and efficacy of fesoterodine 4 mg and 8 mg following once daily treatment for 12 weeks in pediatric neurogenic detrusor overactivity (NDO) subjects with weight >25 kg.
	To determine the safety and efficacy of fesoterodine 2 mg and 4 mg following once daily treatment for 12 weeks in pediatric NDO subjects with weight ≤25 kg.
Secondary	
Safety, Efficacy	Evaluate the safety and efficacy of fesoterodine versus oxybutynin in pediatric NDO subjects with weight >25 kg.
Safety	Evaluate the safety of fesoterodine 4 mg and 8 mg once daily treatment for up to 24 weeks in pediatric NDO subjects with weight >25 kg.
	Evaluate the safety of fesoterodine 2 mg and 4 mg once daily treatment for up to 24 weeks in pediatric NDO subjects with weight ≤25 kg.
PK	Determine the steady-state population pharmacokinetics (PK) of 5-hydroxymethyltolterodine (5-HMT) following fesoterodine 4 mg and 8 mg once daily treatment in pediatric NDO subjects with weight >25 kg.
	Determine the steady-state population PK of 5-HMT following treatment with 2 doses of fesoterodine 2 mg and 4 mg once daily in pediatric NDO subjects.

Cohort 1 (weight >25 kg) treatment: fesoterodine prolonged release (PR) 4 or 8 mg tablet or oxybutynin extended release (XL) tablet
Cohort 2 (weight ≤25 kg) treatment: fesoterodine 2 or 4 mg beads-in-capsule (BIC)

Table S2.   Study Endpoints

Type	Endpoint
Primary	
Efficacy	Maximum cystometric bladder capacity defined as maximal tolerable cystometric capacity or until voiding/leaking begins or at 40 cm H_2O
Secondary	
Efficacy	• Detrusor pressure at maximum bladder capacity • Presence of involuntary detrusor contraction (IDC) • Bladder volume at first IDC • Bladder compliance • Mean number of micturitions per 24 hours • Mean number of catheterizations per 24 hours • Mean number of micturitions and catheterizations combined per 24 hours • Mean number of incontinence episodes per 24 hours • Mean urgency episodes per 24 hours if applicable (only for sensate subjects) • Mean volume voided per micturition • Mean volume per catheterization • Mean volume voided per micturition or catheterization

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Table S2. Study Endpoints

Type	Endpoint

Safety	• Adverse events, including monitoring of targeted events including, but not limited to:
	  • 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, somnolence
	  • Visual effects such as accommodation disorder, blurred vision, and amblyopia
	• Visual acuity and accommodation tests
	• Cognitive function by the Childhood Behavior Checklist and Grooved Pegboard Test
	• 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 in subjects not performing clean intermittent catheterization, or with >1 UTI during the study
	• Physical examination and weight

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

METHODS

Study Design:

For Cohort 1 (weight >25 kg), this was a randomized, open-label, active comparator, parallel group study with 3 treatment arms. The study consisted of 2 parts: a 12-week, 3-arm phase with an active comparator (oxybutynin extended release [XL]), followed by a 12-week, 2-arm extension phase without the active comparator.

There was a variable screening period (minimum 3 days) prior to the baseline visit, the duration of which was principally determined by the prior medication subjects may have needed to washout. At baseline, subjects were randomized in a 1:1:1 ratio to one of 3 arms: 4 or 8 mg per day of fesoterodine or oxybutynin XL. Subjects were stratified at randomization into 2 groups dependent on their body weight. The lower weight group within Cohort 1 included all those with a weight of 50 kg or less, and the higher weight group within Cohort 1 included all those above 50 kg.

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

For Cohort 2 (weight ≤25 kg), the study consisted of 2 parts: a 12-week, 2-arm Efficacy Phase, followed by a 12-week, 2-arm Safety Extension Phase.

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There was a variable screening period (minimum 3 days) prior to the baseline visit, the duration of which was principally determined by the prior medication subjects may have needed to washout. At baseline, subjects were randomized in a 1:1 ratio to one of 2 fesoterodine beads-in-capsule (BIC) treatment arms: 2 or 4 mg per day.

It was planned that a sufficient number of subjects were to be randomized into Cohort 2 to ensure a total of approximately 50 subjects (approximately 25 evaluable subjects per arm) were evaluable for the primary efficacy and safety analyses at Week 12.

Diagnosis and Main Criteria for Inclusion: The study population consisted of subjects aged 6 to 17 years, with stable neurological disease and clinically or urodynamically demonstrated neurogenic detrusor overactivity (NDO), no history of indwelling catheter within 4 weeks of participation in the study, no history of autonomic dysreflexia, and no clinically significant urinary tract infection (UTI) at screening. Subjects not requiring intermittent catheterization who had a post-void residual (PVR) volume greater than 20 mL as determined by transabdominal ultrasound immediately after urination were excluded.

Study Treatment:

Fesoterodine

Subjects randomized to fesoterodine in Cohort 1 (weight >25 kg) received either 4 or 8 mg fesoterodine prolonged release (PR) tablets once daily throughout the initial 12 weeks of the Active Comparator Phase and continued at the same dose during the 12-week Safety Extension Phase. All those assigned to the fesoterodine 8 mg arm started at 4 mg daily for 1 week, and then escalated to 8 mg daily.

Subjects in Cohort 2 (weight ≤25 kg) were randomized to either 2 or 4 mg fesoterodine BIC capsules once daily throughout the initial 12 weeks of the Efficacy Phase and continued at the same dose during the 12-week Safety Extension Phase. All those assigned to the fesoterodine 4 mg arm started at 2 mg daily for 1 week and then escalated to 4 mg daily.

If subjects could not tolerate the doses they were randomized to, they were to be withdrawn from the study, as a dose reduction was not permitted on this study.

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Oxybutynin

Subjects in Cohort 1 (weight >25 kg) randomized to oxybutynin received oxybutynin XL tablets at a starting dose in accordance with approved pediatric labeling and accepted practice (eg, oxybutynin XL 5 mg once a day). Dose optimization was achieved by either up or down titration in 5-mg increments on an approximately weekly basis to achieve a balance of efficacy and tolerability. All subjects should have achieved a minimum total daily dose of oxybutynin XL 10 mg by the end of the dose adjustment period at Week 4. The maximum dose used in this study did not exceed the recommended dose consistent with approved pediatric labeling and accepted practice. Subjects who were on oxybutynin prior to study entry and who were randomized to the oxybutynin XL treatment group may have, at the discretion of the investigator, restarted at the equivalent pre-study total daily dose.

After Week 4, subjects taking oxybutynin XL remained on the same dose for the subsequent 8 weeks of the study, and no further dose adjustments were permitted. Subjects who were unable to tolerate a minimum total dose of oxybutynin XL 10 mg once daily were to be withdrawn. Subjects who withdrew from the oxybutynin treatment arm for reasons of toleration, and who fulfilled all continuation criteria, may have been directly allocated by the investigator to fesoterodine treatment at either 4 or 8 mg per day for the remaining 12-week Safety Extension Phase. All those assigned to the fesoterodine 8 mg arm started at 4 mg daily for 1 week, and then escalated to 8 mg daily.

At Visit 5 (or earlier if appropriate), subjects in the oxybutynin arm of the study were allocated by the investigator to fesoterodine at either 4 or 8 mg per day. Subjects underwent a minimum 2-day washout period from oxybutynin prior to starting treatment with fesoterodine. All those assigned to the fesoterodine 8 mg arm started at 4 mg daily for 1 week and then escalated to 8 mg daily. Once allocated, the dose remained fixed for the period of the extension; if treatment was inadequate or the subject could not tolerate the dose, consideration was to be given to withdrawal.

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Table S3.   Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form Capsule
Fesoterodine Fumarate PR	8394601 86552001 89162001 15-003448/ E10453930U	11-006370 12-003817 13-111228 15-005055	4 mg	Film-coated Tablet
Fesoterodine Fumarate PR	8414101 86824001 89098001 15-003487/ E10432130U	11-006371 12-004327 13-111229 15-005056	8 mg	Film-coated Tablet
Fesoterodine Fumarate	SW-SDM	15-007270	2 mg	Controlled Release Capsule
Fesoterodine Fumarate	SW-SDM	15-007271	4 mg	Controlled Release Capsule
Oxybutynin Chloride Extended Release	1060901 1084901 125185P1 83889P2	11-006670 12-000006 14-001712 13-107177	5 mg	Tablet
Oxybutynin Chloride Extended Release	1064501 1106801 125299P2 83890P1	11-006671 12-000007 14-002192 13-107547	10 mg	Tablet
Oxybutynin HCl Prolonged Release	BHLS000 BHLS001 CDLS000 CHLS201 DBZSA00 DKBS000 EABS003 EFZS000	12-000223 12-001581 12-005876 13-107832 13-109719 14-001862 14-003633 14-006148	5 mg	Tablet
Oxybutynin HCl Prolonged Release	CALS601 CFLS103 CHZS100 DBZSB00 DKZSA00 DLBS001 EGZSE02 BHLS200 BHLS200	12-003396 12-005870 13-107831 13-109741 14-001749 14-003631 14-006149 12-001582 12-000225	10 mg	Tablet

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Efficacy Evaluations:

Urodynamic assessment was performed at Visit 2 (baseline) and Visit 5 (Week 12). The following were 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 involuntary detrusor contractions (IDC).

- Bladder volume at first IDC, if present.

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

- Presence of subtraction test (eg, cough) on urodynamic trace.

For all subjects, eligibility for study entry or continuation on the basis of urodynamic criteria were verified by a central reader.

At Visit 5 (or end of Active Comparator/Efficacy Phase), subjects who demonstrated a clinically relevant increased detrusor pressure, or other urodynamic findings suggestive of worsening condition compared to baseline, were not allowed to continue into the Safety Extension Phase. In this case, consideration was to be given to imaging of upper urinary tract (for example, videourodynamics or ultrasound) according to accepted local standard of care in subjects with vesicoureteral reflux, or other conditions that predispose to upper urinary tract dysfunction or damage.

A bladder diary was completed for 3 consecutive days (with a minimum of 2 days) during the week prior to Visit 2 (baseline) and Visit 5 (Week 12), using an electronic capture device. Completion of the bladder diary prior to Visit 2 (baseline) was to begin only after previous treatment with prohibited concomitant medications had undergone a minimum washout appropriate to the drug so any clinical effect was at a minimum (eg, 3-day minimum washout for oxybutynin, 7-day minimum washout for darifenacin and solifenacin). Daily micturition or catheterization frequency, volume of urine from each micturition or catheterization (for one of the days), incontinence episodes and urgency episodes (if appropriate) were recorded.

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Pharmacokinetic Evaluations: At Visit 3 (Week 4), blood samples were collected from each subject assigned to receive fesoterodine for the analysis of 5-hydroxymethyltolterodine (5-HMT). Samples were analyzed for 5-HMT using a validated liquid chromatography/tandem mass spectrometry method in compliance with Pfizer standard operating procedures.

Safety Evaluations: Safety evaluations included adverse events (AEs), vital signs, physical examinations, clinical laboratory tests, weight measurements, visual acuity and accommodation, electrocardiogram, PVR urine volume, Childhood Behavior Checklist (CBCL), Grooved Pegboard Test (GPT), and pregnancy testing.

Statistical Methods:

Efficacy

The following hypotheses are applicable only to the analyses of the heavier (>25 kg) Cohort 1, as there was no formal hypothesis testing planned for the lighter (≤25 kg) Cohort 2.

Null Hypothesis: The difference between baseline and Week 12 in maximum cystometric bladder capacity is equal to zero.

Alternative Hypothesis: The difference between baseline and Week 12 in maximum cystometric bladder capacity is not equal to zero.

Changes from baseline in Cohort 1 were tested at the $\alpha=0.05$ level, and 95% confidence intervals (CIs) were estimated for Cohort 2.

Cohort 1 Primary Efficacy Analysis

Change from baseline to Week 12 in the primary endpoint was analyzed using an analysis of covariance (ANCOVA) including terms for treatment group, baseline (for the endpoint being analyzed) and baseline weight. The least squares (LS) mean change from baseline for each treatment group, standard error (SE), 95% CIs and p-values associated with the LS mean changes from baseline were presented.

The following primary comparisons of interest were assessed:

- Change from baseline to Week 12 for fesoterodine 4 mg PR.

- Change from baseline to Week 12 for fesoterodine 8 mg PR.

The LS means and 95% CIs for the difference between each fesoterodine dose group and oxybutynin were also calculated.

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The following secondary comparisons were assessed using 95% CIs for the difference between treatment means (for the change from baseline to Week 12):

- Fesoterodine 4 mg PR versus oxybutynin.

- Fesoterodine 8 mg PR versus oxybutynin.

As these secondary comparisons were based on an estimation approach, no formal statistical hypothesis testing was performed. Conclusions were based on point estimates and CIs.

The primary analysis was based on the Cohort 1 Full Analysis Set (FAS).

Cohort 2 Primary Efficacy Analysis

Change from baseline to Week 12 in the primary endpoint was analyzed using an ANCOVA including terms for treatment group and baseline (for the endpoint being analyzed). The LS mean change from baseline for each treatment group, standard error and 95% CIs associated with the LS mean changes from baseline were presented.

The following primary comparisons of interest were assessed:

- Change from baseline to Week 12 for fesoterodine 2 mg BIC.

- Change from baseline to Week 12 for fesoterodine 4 mg BIC.

As these comparisons were based on an estimation approach, no formal statistical hypothesis testing was performed. Conclusions were based on point estimates and CIs.

The primary analysis was based on the Cohort 2 FAS.

For the FAS analysis, a baseline observation carried forward (BOCF) and a last observation carried forward (LOCF) algorithm were used for missing data.

Secondary Efficacy Analyses

All secondary endpoints were analyzed as for the primary analyses as defined for each respective cohort using the appropriate FAS.

The presence of IDC was presented using cell counts and proportions for each response category. For summaries of change from baseline, the tables were presented as a cross tabulation with baseline visit along the side and Week 12 results along the top.

Safety

Tables of safety and demographic data, including AEs and medical history were reported in accordance with current Pfizer standards and were presented separately for each cohort.

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For treatment-emergent AEs (TEAEs) which occurred during the Active Comparator or Efficacy Phases of the study for each cohort, 3-tier AE reporting was used:

- Tier 1 AEs: AEs identified as targeted medical events in the safety review plan

- Tier 2 AEs: AEs that occurred in 4 or more subjects in any treatment group

- Tier 3 AEs: AEs that were not tier 1 or tier 2 (Tier 3 AEs were not summarized separately)

For Cohort 1, the treatment comparisons were fesoterodine 4 mg versus oxybutynin and fesoterodine 8 mg versus oxybutynin. The risk difference was calculated as fesoterodine (4 mg PR or 8 mg PR) minus oxybutynin. There were no treatment comparisons presented for Cohort 2, as there was no active comparator for this cohort.

The frequency and percentage of subjects for all AEs were presented by treatment group, separately for the Active Comparator, Efficacy, and Safety Extension Phases and over the entire study.

For vital signs, change from baseline was summarized together with the number of subjects whose blood pressure and heart rate fell outside specified ranges. Furthermore, the number of subjects whose decreases and increases in blood pressure fell outside specified ranges was summarized.

Visual acuity (LogMAR units) and accommodation (the distance for each eye at which vision becomes blurred – the mean of triplicate measurements), CBCL (Domain T Scores and Total Scores as captured in the case report form [CRF]), GPT (time to completion, number of pegs dropped, and number of pegs correctly placed – by dominant/non-dominant hand and whether the 10-peg or 25-peg test was used, separately), physical examination, and weight were summarized by visit and changes from baseline at each visit using descriptive statistics. For visual acuity, LogMAR units were derived from the Snellen ratios recorded on the CRF.

Pharmacokinetics

Plasma concentrations of 5-HMT were listed and summarized for subjects in the pharmacokinetic (PK) analysis set (for each cohort separately).

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A population PK modeling approach was used to analyze the plasma concentration-time data following fesoterodine administration for the estimation of population PK parameters (apparent oral clearance [CL/F], absorption rate constant [Ka], and volume of distribution [Vd]) of 5-HMT in pediatric subjects in this study. Different structural models such as 1- or 2-compartment PK models with first-order absorption were considered as dictated by the data. In all models, estimation of CL/F and apparent volume of distribution (Vd/F) were of primary interest. A base model was constructed with a priori allometric weight scaling factor on CL/F and Vd/F, with clearance and volume parameters being scaled with body weight raised to power coefficients. In addition, the effect of drug formulation on some parameters related to absorption (eg, absolute oral bioavailability [F], Ka) was also investigated. In full model development, predefined covariate-parameter relationships (ie, the effects of gender and CYP2D6 metabolizer status, as predictors of CL/F and Vd/F) were identified based on exploratory graphics. These covariates are selected from those which were found in the prior adult population analysis. However, age was not included in this full model, because age was considered to be a potential confounding factor in the relationship between body weight and PK parameters.

RESULTS

Subject Disposition and Demography:

Cohort 1

Overall, a higher proportion of subjects randomized to fesoterodine 4 mg discontinued from the study (12 subjects [28.6%]) than those randomized to fesoterodine 8 mg (6 subjects [14.3%]) or oxybutynin (5 of 40 subjects [12.5%], 1 of these discontinued from the study while receiving fesoterodine 4 mg in the Safety Extension Phase), with the most common reasons being AE and withdrawal by parent/guardian (Figure S1).
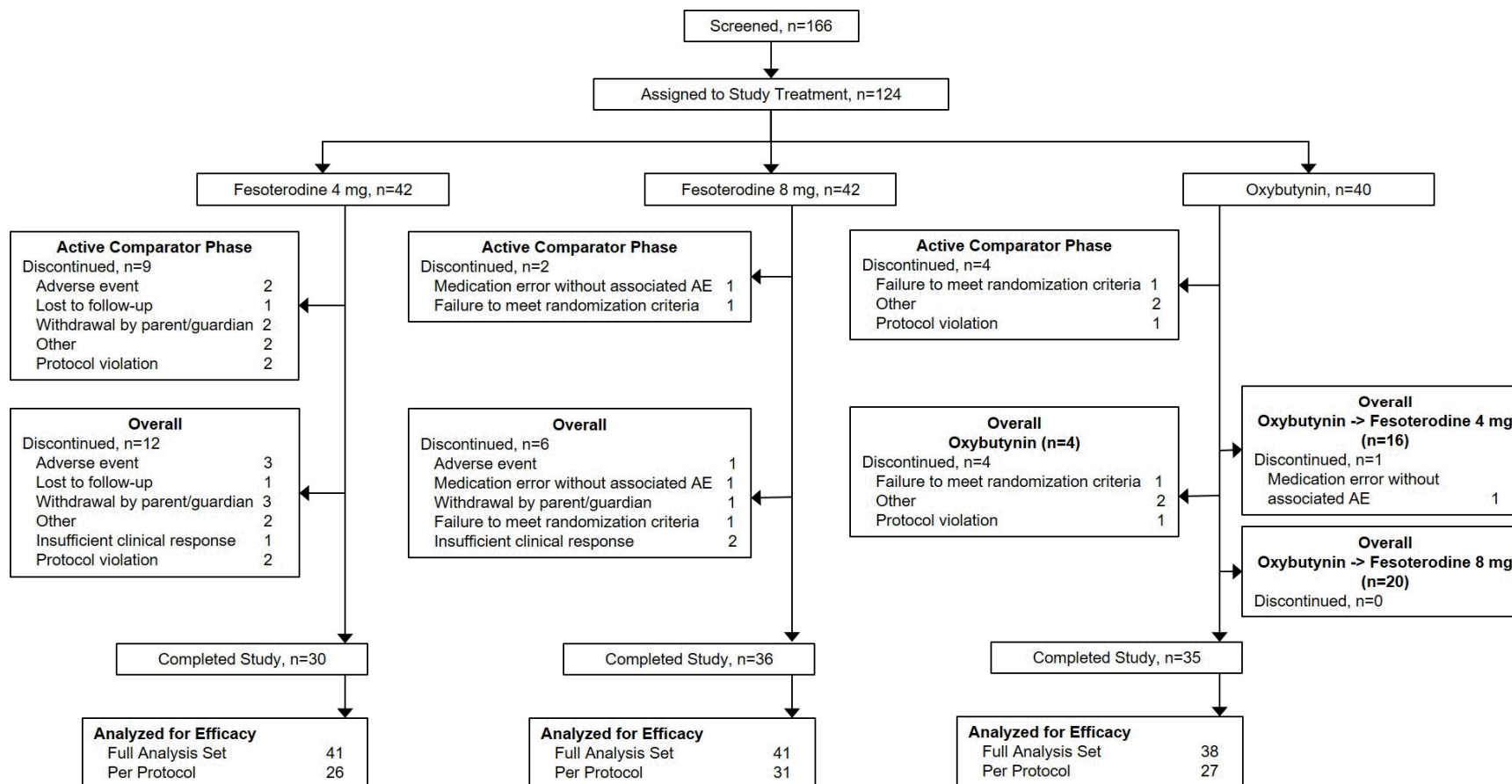
In the Active Comparator Phase, a higher proportion of subjects discontinued from the study in the fesoterodine 4 mg arm (9 subjects [21.4%]) than the fesoterodine 8 mg arm (2 subjects [4.8%]) or the oxybutynin arm (4 subjects [10.0%]).

In the fesoterodine 4 mg arm, the majority of discontinuations from the study occurred during the Active Comparator Phase (9 subjects), with 3 subjects discontinuing from the study after completing the Active Comparator Phase.

In Cohort 1, 6 subjects (15.0%) permanently discontinued treatment with oxybutynin during the Active Comparator Phase. Two of these subjects continued into the Safety Extension Phase; therefore, they did not discontinue from the study during the Active Comparator Phase, as allowed per the protocol for subjects randomized to oxybutynin. In the Safety Extension Phase, these 2 subjects received fesoterodine and completed the study. The other 4 subjects discontinued from the study during the Active Comparator Phase.

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Figure S1. Disposition Flow Chart - Cohort 1

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                              ┌──────────────────────┐
                              │   Screened, n=166    │
                              └──────────────────────┘
                                         │
                              ┌───────────────────────────────┐
                              │ Assigned to Study Treatment,   │
                              │           n=124               │
                              └───────────────────────────────┘
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Fesoterodine 4 mg, n=42	Fesoterodine 8 mg, n=42	Oxybutynin, n=40

Active Comparator Phase
Discontinued, n=9
  Adverse event   2
  Lost to follow-up   1
  Withdrawal by parent/guardian   2
  Other   2
  Protocol violation   2

Active Comparator Phase
Discontinued, n=2
  Medication error without associated AE   1
  Failure to meet randomization criteria   1

Active Comparator Phase
Discontinued, n=4
  Failure to meet randomization criteria   1
  Other   2
  Protocol violation   1

Overall
Discontinued, n=12
  Adverse event   3
  Lost to follow-up   1
  Withdrawal by parent/guardian   3
  Other   2
  Insufficient clinical response   1
  Protocol violation   2

Overall
Discontinued, n=6
  Adverse event   1
  Medication error without associated AE   1
  Withdrawal by parent/guardian   1
  Failure to meet randomization criteria   1
  Insufficient clinical response   2

**Overall
Oxybutynin (n=4)**
Discontinued, n=4
  Failure to meet randomization criteria   1
  Other   2
  Protocol violation   1

**Overall
Oxybutynin -> Fesoterodine 4 mg
(n=16)**
Discontinued, n=1
  Medication error without
  associated AE   1

**Overall
Oxybutynin -> Fesoterodine 8 mg
(n=20)**
Discontinued, n=0

Completed Study, n=30	Completed Study, n=36	Completed Study, n=35

Analyzed for Efficacy
  Full Analysis Set   41
  Per Protocol   26

Analyzed for Efficacy
  Full Analysis Set   41
  Per Protocol   31

Analyzed for Efficacy
  Full Analysis Set   38
  Per Protocol   27

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For Cohort 1, demographic and baseline characteristics (age, ethnicity, and weight) were generally well balanced between treatment arms, but there were more male subjects (n=26) than female subjects (n=16) in the fesoterodine 4 mg arm and more male subjects (n=23) than female subjects (n=17) in the oxybutynin arm. Additionally, the proportion of white subjects was lower in the oxybutynin arm than in the fesoterodine arms, and the proportion of Asian subjects was higher in the oxybutynin arm than in the fesoterodine arms. The mean weight was 43.26, 42.02, and 43.20 kg and the mean age was 10.74, 11.02, and 11.15 years for the fesoterodine 4 mg, fesoterodine 8 mg, and oxybutynin arms, respectively.

Cohort 2

Overall, a higher proportion of subjects discontinued from the study in the fesoterodine 2 mg BIC arm (8 subjects [28.6%]) than in the fesoterodine 4 mg BIC arm (1 subject [3.4%]), with the most common reasons being AE and withdrawal by parent/guardian (Figure S2).

In the Efficacy Phase, a higher proportion of subjects discontinued the study in the fesoterodine 2 mg BIC arm (7 subjects [25.0%]) than in the fesoterodine 4 mg BIC arm (1 subject [3.4%]).

In the fesoterodine 2 mg BIC arm, the majority of discontinuations occurred during the Efficacy Phase, with only 1 subject discontinuing from the study after completing the Efficacy Phase. In the fesoterodine 4 mg BIC arm, 1 subject discontinued from the study during the Efficacy Phase, and no subjects discontinued from the study after completing the Efficacy Phase.

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Figure S2. Disposition Flow Chart - Cohort 2

For Cohort 2, demographic and baseline characteristics (age, ethnicity, and weight) were generally well balanced between treatment arms, but there were more male subjects (n=16) than female subjects (n=12) in the fesoterodine 2 mg BIC arm and more female subjects (n=19) than male subjects (n=10) in the fesoterodine 4 mg BIC arm. The mean weight was 21.1 and 21.3 kg and the mean age was 7.5 and 7.9 years for the fesoterodine 2 and 4 mg BIC arms, respectively, as expected given the weight constraint of Cohort 2.

There were more Asian subjects than white subjects in both fesoterodine BIC treatment arms, which is consistent with the higher enrollment at sites in Asian countries than in all other countries.

Efficacy Results:

For Cohort 1, changes from baseline were tested at the $\alpha=0.05$ significance level. Therefore, results with $p \leq 0.05$ are described as significant changes from baseline (improvements, increases, or decreases), and results with $p > 0.05$ are described as numerical changes from baseline (improvements, increases, or decreases).

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For Cohort 2, 95% CIs were estimated for the mean changes from baseline. Therefore, results for which the 95% CI excluded zero are described as improvements, increases or decreases from baseline, whereas, results for which the 95% CI included zero are described as numerical changes from baseline (improvements, increases, or decreases).

Primary Efficacy Analysis

For Cohort 1 (subjects >25 kg), treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in significant increases from baseline to Week 12 in **maximum cystometric bladder capacity** (p=0.0001, p<0.0001, and p<0.0001, respectively; Table S4). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

Table S4. Statistical Analysis of Change from Baseline in Maximum Cystometric Bladder Capacity (ml) at Week 12 - Full Analysis Set - Cohort 1

		Feso 4mg (N=41)	Feso 8mg (N=41)	Oxybutynin (N=38)
WEEK 12	N	41	41	38
	LS Mean (SE)	58.12 (14.78)	83.36 (14.71)	87.17 (15.33)
	95% CI for mean	(28.84,87.39)	(54.22,112.49)	(56.82,117.53)
	P-value	0.0001	<.0001	<.0001
	Versus Oxybutynin			
	LS Mean (SE)	-29.06 (21.39)	-3.82 (21.23)	
	95% CI for mean	(-71.42,13.31)	(-45.87,38.23)	

Baseline is defined as the last available measurement prior to the start of treatment.
Based on an ANCOVA model with terms for treatment group, baseline (for the endpoint being analyzed) and baseline weight.
LOCF/BOCF was used for imputing missing values.
PFIZER CONFIDENTIAL SDTM Creation: 09MAR2020 (08:02) Source Data: ADUR Output File:
./CDISC/A0221047/desc_infr_chg_ur_mbc_1 Date of Generation: 07APR2020 (13:46)
Table 14.2.2.1a is for Pfizer internal use.

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For Cohort 2 (subjects ≤25 kg), treatment with fesoterodine 2 and 4 mg BIC resulted in increases from baseline to Week 12 in **maximum cystometric bladder capacity**, with 95% CIs for the mean change from baseline excluding zero (Table S5).

Table S5.		Statistical Analysis of Change from Baseline in Maximum Cystometric Bladder Capacity (ml) at Week 12 - Full Analysis Set - Cohort 2	
		Fesoterodine 2mg BIC (N=25)	Fesoterodine 4mg BIC (N=28)
WEEK 12	N	25	28
	LS Mean (SE)	23.49 (10.18)	40.17 (9.62)
	95% CI for mean	(3.03,43.95)	(20.84,59.50)

Baseline is defined as the last available measurement prior to the start of treatment. Based on an ANCOVA model with terms for treatment group,
baseline (for the endpoint being analyzed) and baseline weight.
LOCF/BOCF was used for imputing missing values.
BIC= Beads-in-Capsule.
PFIZER CONFIDENTIAL SDTM Creation: 03MAR2020 (05:17) Source Data: ADUR Output File:
./CDISC/A0221047_CH2/desc_infr_chg_ur_mbc_1_c2 Date of Generation: 07APR2020 (09:49)
Table 14.2.2.1b is for Pfizer internal use.

Secondary Efficacy Analyses

- **Detrusor Pressure at Maximum Bladder Capacity:**

  For Cohort 1 (subjects >25 kg), treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in numerical decreases from baseline to Week 12 in detrusor pressure at maximum bladder capacity (LS mean [SE]: -2.86 cm H_2O [2.39], p=0.2334; LS mean [SE]: -1.57 cm H_2O [2.37], p=0.5087; and LS mean [SE]: -2.39 cm H_2O [2.46], p=0.3333, respectively). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2 (subjects ≤25 kg), treatment with fesoterodine 4 mg BIC resulted in a decrease from baseline to Week 12 in detrusor pressure at maximum bladder capacity (LS mean [SE]: -9.73 cm H_2O [3.71]), with the 95% CI for the mean change from baseline excluding zero. Treatment with fesoterodine 2 mg BIC resulted in a numerical decrease from baseline to Week 12 in detrusor pressure at maximum bladder capacity (LS mean [SE]: -2.74 cm H_2O [3.92]), with the 95% CI for the mean change from baseline including zero.

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- **Presence of Involuntary Detrusor Contractions:**

  For Cohort 1, a numerically higher proportion of subjects showed improvement from baseline to Week 12 for the presence of IDC in the fesoterodine 8 mg arm (18 subjects [43.9%]) than the fesoterodine 4 mg arm (9 subjects [22.0%]). Fewer than 5% of subjects in any treatment arm worsened from baseline to Week 12.

  For Cohort 2, a numerically higher proportion of subjects showed improvement from baseline to Week 12 for the presence of IDC in the fesoterodine 4 mg BIC arm (11 subjects [39.3%]) than the fesoterodine 2 mg BIC arm (6 subjects [24.0%]). No subjects in either treatment arm worsened from baseline to Week 12.

- **Bladder Volume at First Involuntary Detrusor Contraction:**

  For Cohort 1, treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in a significant increases from baseline to Week 12 in bladder volume at first IDC (LS mean [SE]: 30.53 mL [14.15], p=0.0336; LS mean [SE]: 26.06 mL [12.01], p=0.0327; and LS mean [SE]: 41.31 mL [12.78], p=0.0017, respectively). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2, treatment with fesoterodine 4 mg BIC resulted in an increase from baseline to Week 12 in bladder volume at first IDC (LS mean [SE]: 31.26 mL [12.14]), with the 95% CI for the mean change from baseline excluding zero. Treatment with fesoterodine 2 mg BIC resulted in a numerical increase from baseline to Week 12 in bladder volume at first IDC (LS mean [SE]: 23.80 mL [12.63]), with the 95% CI for the mean change from baseline including zero.

- **Bladder Compliance:**

  For Cohort 1, treatment with fesoterodine 4 and 8 mg resulted in numerical increases from baseline to Week 12 in bladder compliance (LS mean [SE]: 6.40 mL/cm H_2O [3.47], p=0.0679 and LS mean [SE]: 5.41 mL/cm H_2O [3.48], p=0.1233, respectively). Treatment with oxybutynin resulted in a significant increase from baseline to Week 12 in bladder compliance (LS mean [SE]: 11.36 mL/cm H_2O [3.56], p=0.0019). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2, treatment with fesoterodine 4 mg BIC resulted in an increase from baseline to Week 12 in bladder compliance (LS mean [SE]: 16.44 mL/cm H_2O [6.15]), with the 95% CI for the mean change from baseline excluding zero. Treatment with fesoterodine 2 mg BIC resulted in a numerical increase from baseline to Week 12 in bladder compliance (LS mean [SE]: 12.44 mL/cm H_2O [6.51]), with the 95% CI for the mean change from baseline including zero.

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- **Mean Number of Micturitions per 24 Hours:**

  For Cohort 1, treatment with fesoterodine 4 mg and oxybutynin resulted in significant decreases from baseline to Week 12 in the mean number of micturitions per 24 hours (LS mean [SE]: -1.07 [0.41], p=0.0116 and LS mean [SE]: -0.97 [0.34], p=0.0061, respectively). Treatment with fesoterodine 8 mg resulted in a numerical decrease from baseline to Week 12 in the mean number of micturitions per 24 hours (LS mean [SE]: -0.68 [0.38], p=0.0765). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2, treatment with fesoterodine 4 mg BIC resulted in a decrease from baseline to Week 12 in the mean number of micturitions per 24 hours (LS mean [SE]: -0.70 [0.32]), with the 95% CI for the mean change from baseline excluding zero. Treatment with fesoterodine 2 mg BIC resulted in a numerical decrease from baseline to Week 12 in the mean number of micturitions per 24 hours (LS mean [SE]: -0.37 [0.35]), with the 95% CI for the mean change from baseline including zero.

- **Mean Number of Catheterizations per 24 Hours:**

  For Cohort 1, treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in numerical decreases from baseline to Week 12 in the mean number of catheterizations per 24 hours (LS mean [SE]: -0.30 [0.17], p=0.0787; LS mean [SE]: -0.32 [0.18], p=0.0727; and LS mean [SE]: -0.34 [0.18], p=0.0666; respectively). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  Treatment with fesoterodine 2 and 4 mg BIC resulted in numerical decreases from baseline to Week 12 in the mean number of catheterizations per 24 hours (LS mean [SE]: -0.10 [0.20] and -0.22 [0.19], respectively), with the 95% CIs for the mean change from baseline including zero.

- **Mean Number of Micturitions or Catheterizations Combined per 24 Hours:**

  For Cohort 1, treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in significant decreases from baseline to Week 12 in the mean number of micturitions and catheterizations combined per 24 hours (LS mean [SE]: -0.61 [0.24], p=0.0111; LS mean [SE]: -0.60 [0.25], p=0.0171; and LS mean [SE]: -0.75 [0.24], p=0.0028; respectively). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  Treatment with fesoterodine 2 and 4 mg BIC resulted in numerical decreases from baseline to Week 12 in the mean number of micturitions and catheterizations combined per 24 hours (LS mean [SE]: -0.24 [0.21] and -0.28 [0.20], respectively), with the 95% CIs for the mean change from baseline including zero.

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- **Mean Number of Incontinence Episodes per 24 Hours:**

  For Cohort 1, treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in significant decreases from baseline to Week 12 in the mean number of incontinence episodes per 24 hours (LS mean [SE]: -0.46 [0.23], p=0.0496; LS mean [SE]: -0.89 [0.23], p=0.0002; and LS mean [SE]: -1.01 [0.23], p<0.0001; respectively). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2 (subjects ≤25 kg), treatment with fesoterodine 4 mg BIC resulted in a decrease from baseline to Week 12 in the mean number of incontinence episodes per 24 hours (LS mean [SE]: -0.69 [0.30]), with the 95% CI for the mean change from baseline excluding zero. Treatment with fesoterodine 2 mg BIC resulted in a numerical decrease from baseline to Week 12 in the mean number of incontinence episodes per 24 hours (LS mean [SE]: -0.38 [0.29]), with the 95% CI for the mean change from baseline including zero.

- **Mean Number of Urgency Episodes per 24 Hours:**

  For Cohort 1, treatment with fesoterodine 4 mg resulted in a significant decrease from baseline to Week 12 in the mean number of urgency episodes per 24 hours (LS mean [SE]: -0.62 [0.28], p=0.0298). Treatment with fesoterodine 8 mg and oxybutynin resulted in numerical decreases from baseline to Week 12 in the mean number of urgency episodes per 24 hours (LS mean [SE]: -0.50 [0.33], p=0.1417 and LS mean [SE]: -0.14 [0.28], p=0.6219, respectively). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2, treatment with fesoterodine 2 and 4 mg BIC resulted in numerical decreases from baseline to Week 12 in the mean number of urgency episodes per 24 hours (LS mean [SE]: -0.23 [0.29] and -0.62 [0.35], respectively), with the 95% CIs for the mean change from baseline including zero.

- **Mean Volume Voided per Micturition:**

  For Cohort 1, treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in numerical increases from baseline to Week 12 in the mean volume voided per micturition (LS mean [SE]: 4.10 mL [15.96], p=0.7986; LS mean [SE]: 19.21 mL [15.83], p=0.2313; and LS mean [SE]: 4.15 mL [13.32], p=0.7571; respectively). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2, treatment with fesoterodine 2 and 4 mg BIC resulted in numerical decreases from baseline to Week 12 in the mean volume voided per micturition (LS mean [SE]: -12.72 mL [10.37] and -8.41 mL [9.26], respectively), with the 95% CIs for the mean change from baseline including zero.

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- **Mean Volume per Catheterization:**

  For Cohort 1, treatment with fesoterodine 8 mg and oxybutynin resulted in significant increases from baseline to Week 12 in the mean volume per catheterization (LS mean [SE]: 47.18 mL [16.33], p=0.0048 and LS mean [SE]: 45.90 mL [17.45], p=0.0100, respectively). Treatment with fesoterodine 4 mg resulted in a numerical increase from baseline to Week 12 in the mean volume per catheterization (LS mean [SE]: 29.47 mL [15.53], p=0.0610). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2, treatment with fesoterodine 2 and 4 mg BIC resulted in numerical increases from baseline to Week 12 in the mean volume per catheterization (LS mean [SE]: 11.50 mL [10.60] and 1.74 mL [10.17], respectively), with the 95% CIs for the mean change from baseline including zero.

- **Mean Volume Voided per Micturition or Catheterization:**

  For Cohort 1, treatment with fesoterodine 8 mg and oxybutynin resulted in significant increases from baseline to Week 12 in the mean volume voided per micturition or catheterization (LS mean [SE]: 55.55 mL [15.01], p=0.0003 and LS mean [SE]: 36.69 mL [15.01], p=0.0161, respectively). Treatment with fesoterodine 4 mg resulted in a numerical increase from baseline to Week 12 in the mean volume voided per micturition or catheterization (LS mean [SE]: 18.45 mL [15.11], p=0.2246). The 95% CIs for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

  For Cohort 2, treatment with fesoterodine 2 mg BIC resulted in a numerical increase from baseline to Week 12 in the mean volume voided per micturition or catheterization (LS mean [SE]: 7.12 mL [9.44]), with the 95% CI for the mean change from baseline including zero. Treatment with fesoterodine 4 mg BIC resulted in a numerical decrease from baseline to Week 12 in the mean volume voided per micturition or catheterization (LS mean [SE]: -2.65 mL [8.74]), with the 95% CI for the mean change from baseline including zero.

Pharmacokinetic Results:

One hundred twenty-one patients from this study were included in the PK analysis. A total of 163 and 112 PK observations were collected from fesoterodine treated patients in Cohort 1 and Cohort 2, respectively.

The 5-HMT plasma concentration data were adequately described by a one-compartment model with first-order absorption and elimination, including a fixed allometric relationship of CL/F and Vd/F, as well as the effect of drug formulation on the extent of absorption (BIC versus tablet).

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The mean (percent relative standard error [%RSE]) for fesoterodine CL/F, fesoterodine Vd/F, and Ka were 71.6 (6.7) L/hour, 68.1 (29.7) L, and 0.0897 (5.99)/hour, respectively. CL/F for subjects with CYP2D6 poor metabolizer (PM) status was estimated to be 0.546 times lower than subjects who are CYP2D6 extensive metabolizers (EMs). Absorption was described with a lag time estimated at 0.285 hours, and the estimated relative bioavailability for BIC compared with tablet was 64.8%.

For Cohort 1, the observed plasma concentrations of 5-HMT in fesoterodine-treated subjects increased proportionally with fesoterodine 4 and 8 mg doses given as the tablet formulation. The observed mean plasma concentrations of 5-HMT appear to increment in a similar way to the increment between different doses.

For Cohort 2, similar to Cohort 1, the plasma concentrations of 5-HMT in fesoterodine-treated subjects increased proportionally with dose, 2 and 4 mg doses given as the BIC formulation. For Cohort 2, mean plasma concentrations of 5-HMT increased in relation to the dose. The plasma 5-HMT concentrations in Cohort 2 following fesoterodine 2 mg BIC once daily were considerably lower and those following fesoterodine 4 mg BIC once daily were generally similar to the concentrations following fesoterodine 4 mg tablet once daily in Cohort 1.

Safety Results:

For Cohort 1 during the Active Comparator Phase, TEAEs were reported for 61.9% of subjects in the fesoterodine 4 mg arm, 47.6% of subjects in the fesoterodine 8 mg arm, and 75.0% of subjects in the oxybutynin arm (Table S6). Serious AEs (SAEs), severe TEAEs, and TEAEs leading to discontinuation from the study or from study drug were reported for fewer than 10% of subjects in any treatment arm.

During the Active Comparator Phase, treatment-related TEAEs were reported for 28.6% of subjects in the fesoterodine 4 mg arm, 23.8% of subjects in the fesoterodine 8 mg arm, and 37.5% of subjects in the oxybutynin arm. There were no treatment-related SAEs, and treatment-related severe TEAEs were reported for 1 subject (2.4%) in the fesoterodine 4 mg arm, no subjects in the fesoterodine 8 mg arm, and 2 subjects (5.0%) in the oxybutynin arm.

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Table S6. Treatment-Emergent AEs (All Causalities) - Safety Analysis Set (Active Comparator Phase) - Cohort 1

Number (%) of Subjects	Feso 4mg n (%)	Feso 8mg n (%)	Oxybutynin n (%)
Subjects evaluable for adverse events	42	42	40
Number of adverse events	80	46	83
Subjects with adverse events	26 (61.9)	20 (47.6)	30 (75.0)
Subjects with serious adverse events	3 (7.1)	2 (4.8)	1 (2.5)
Subjects with severe adverse events	4 (9.5)	1 (2.4)	3 (7.5)
Subjects discontinued from study due to adverse events (a)	3 (7.1)	0	0
Subjects discontinued study drug due to AE and continue Study (b)	0	0	1 (2.5)
Subjects with dose reduced or temporary discontinuation due to adverse events	2 (4.8)	0	2 (5.0)

Includes data up to 7 days after last dose of study drug for subjects who discontinued in the Active Comparator phase, otherwise for subjects continuing into the Safety
Phase, it includes data up to the last dose of study drug in the Active Comparator Phase.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study
MedDRA v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 05MAR2020 (02:33) Source Data: ADAE Output File: ./CDISC/A0221047/adae_s020_1 Date of Generation: 07APR2020 (15:00)
Table 14.3.1.2.1.1a is for Pfizer internal use.

Among subjects who received at least 1 dose of fesoterodine in both the Active Comparator and Safety Extension Phases of Cohort 1, TEAEs were reported for 76.7% of subjects in the fesoterodine 4 mg arm and 62.2% of subjects in the fesoterodine 8 mg arm (Table S7). The incidence of SAEs in the fesoterodine 8 mg arm (10.8%) was numerically higher than in the fesoterodine 4 mg arm (3.3%). The incidence of severe AEs was comparable across fesoterodine treatment arms, and 1 subject in the fesoterodine 8 mg arm discontinued from the study due to an AE.

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Among subjects who received at least 1 dose of fesoterodine in both the Active Comparator and Safety Extension Phases of Cohort 1, treatment-related TEAEs were reported for 33.3% of subjects in the fesoterodine 4 mg arm and 29.7% of subjects in the fesoterodine 8 mg arm. There were no treatment-related SAEs or treatment-related TEAEs leading to discontinuation from the study or from study drug, and treatment-related severe TEAEs were infrequently reported.

Table S7. Treatment-Emergent AEs (All Causalities) - Safety Analysis Set (Overall Fesoterodine 24 Weeks) - Cohort 1

Number (%) of Subjects	Feso 4mg n (%)	Feso 8mg n (%)
Subjects evaluable for adverse events	30	37
Number of adverse events	78	62
Subjects with adverse events	23 (76.7)	23 (62.2)
Subjects with serious adverse events	1 (3.3)	4 (10.8)
Subjects with severe adverse events	2 (6.7)	2 (5.4)
Subjects discontinued from study due to adverse events (a)	0	1 (2.7)
Subjects discontinued study drug due to AE and continue Study (b)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (3.3)	0

Includes data up to 7 days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study
MedDRA v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 05MAR2020 (02:33) Source Data: ADAE Output File:
./CDISC/A0221047/adae_s020_3 Date of Generation: 07APR2020 (15:03)
Table 14.3.1.2.1.3a is for Pfizer internal use.

For Cohort 2 during the Efficacy Phase, TEAEs were reported for 67.9% of subjects in the fesoterodine 2 mg BIC arm and 62.1% of subjects in the fesoterodine 4 mg BIC arm (Table S8). The incidence of SAEs was comparable across both fesoterodine BIC treatment arms, and severe TEAEs occurred infrequently. Three subjects discontinued from the study due to TEAEs in the fesoterodine 2 mg BIC arm, whereas there were no discontinuations from the study due to TEAEs in the fesoterodine 4 mg BIC arm.

During the Efficacy Phase, treatment-related TEAEs were reported for 32.1% of subjects in the fesoterodine 2 mg BIC arm and 10.3% of subjects in the fesoterodine 4 mg BIC arm. There were no treatment-related SAEs or treatment-related severe TEAEs. Treatment-related

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TEAEs leading to discontinuation from the study were reported for 2 subjects (7.1%) in the fesoterodine 2 mg BIC arm.

Table S8. Treatment-Emergent AEs (All Causalities) - Safety Analysis Set (Efficacy Phase) - Cohort 2

Number (%) of Subjects	Fesoterodine 2mg BIC n (%)	Fesoterodine 4mg BIC n (%)
Subjects evaluable for adverse events	28	29
Number of adverse events	40	39
Subjects with adverse events	19 (67.9)	18 (62.1)
Subjects with serious adverse events	2 (7.1)	2 (6.9)
Subjects with severe adverse events	0	1 (3.4)
Subjects discontinued from study due to adverse events (a)	3 (10.7)	0
Subjects discontinued study drug due to AE and continue Study (b)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (3.6)	1 (3.4)

Includes data up to 7 days after last dose of study drug for subjects who discontinued in the efficacy phase, otherwise for subjects continuing into the Safety Phase,
it includes data up to the last dose of study drug in the Efficacy Phase.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study
MedDRA v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 03MAR2020 (05:43) Source Data: ADAE Output File:
./CDISC/A0221047_CH2/adae_s020_1_c2 Date of Generation: 07APR2020 (10:45)
Table 14.3.1.2.1.1b is for Pfizer internal use.

For Cohort 2 during the overall study, TEAEs were reported for 75.0% of subjects in the fesoterodine 2 mg BIC arm and 79.3% of subjects in the fesoterodine 4 mg BIC arm (Table S9). The incidence of severe TEAEs was low, and the incidence of SAEs was comparable between the 2 treatment arms. Three subjects (10.7%) discontinued the study due to TEAEs in the fesoterodine 2 mg BIC arm. The incidence of dose reduction or temporary discontinuations (interruption) of study drug due to TEAEs was low in the 2 arms in Cohort 2.

During the overall study, treatment-related TEAEs were reported for 32.1% of subjects in the fesoterodine 2 mg BIC arm and 10.3% of subjects in the fesoterodine 4 mg BIC arm.

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Table S9. Treatment-Emergent AEs (All Causalities) - Safety Analysis Set (Overall) - Cohort 2

Number (%) of Subjects	Fesoterodine 2mg BIC n (%)	Fesoterodine 4mg BIC n (%)
Subjects evaluable for adverse events	28	29
Number of adverse events	58	58
Subjects with adverse events	21 (75.0)	23 (79.3)
Subjects with serious adverse events	2 (7.1)	3 (10.3)
Subjects with severe adverse events	0	1 (3.4)
Subjects discontinued from study due to adverse events (a)	3 (10.7)	0
Subjects discontinued study drug due to AE and continue Study (b)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (3.6)	1 (3.4)

Includes data up to 7 days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study
MedDRA v22.1 coding dictionary applied.
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./CDISC/A0221047_CH2/adae_s020_3_c2 Date of Generation: 07APR2020 (10:47)
Table 14.3.1.2.1.3b is for Pfizer internal use.

- **Tier 1 Treatment-Emergent Adverse Events:**

  For subjects in Cohort 1 during the Active Comparator Phase, the incidence of Dry mouth was significantly higher in the oxybutynin arm (11 subjects [27.5%]) than in the fesoterodine 4 mg (3 subjects [7.1%]) and fesoterodine 8 mg arms (4 subjects [9.5%]) (p=0.0155 and p=0.0406, respectively). There was no significant difference in the incidence of any other reported Tier-1 TEAE between the oxybutynin arm and the fesoterodine arms.

  For subjects in Cohort 2, the incidence of any reported Tier-1 TEAE was similar (95% CIs for the risk difference included zero) between the fesoterodine 2 and 4 mg BIC arms during the Efficacy Phase.

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- **Tier 2 Treatment-Emergent Adverse Events:**

  For subjects in Cohort 1 during the Active Comparator Phase, the incidence of Dry mouth was numerically higher in the oxybutynin arm (11 subjects [27.5%]) than in the fesoterodine 4 mg (3 subjects [7.1%]) and fesoterodine 8 mg arms (4 subjects [9.5%]) (upper limit of the 95% CI for the risk difference was <0). The incidence of Urinary incontinence was numerically higher in the oxybutynin arm (4 subjects [10.0%]) than in the fesoterodine 8 mg arm (0 subjects) (upper limit of the 95% CI for the risk difference was <0). In addition, the incidence of Viral upper respiratory tract infection was numerically higher in the fesoterodine 4 mg arm (4 subjects [9.5%]) than in the oxybutynin arm (0 subjects) (lower bound of the 95% CI for the risk difference was >0). No TEAEs of Viral upper respiratory tract infection were reported in the fesoterodine 8 mg or oxybutynin arms during the Active Comparator Phase.

  For subjects in Cohort 2, the incidence of any reported Tier-2 TEAE was similar (95% CIs for the risk difference included zero) between the fesoterodine 2 and 4 mg BIC arms during the Efficacy Phase.

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

- **Serious Adverse Events:**

  For subjects in Cohort 1 during the Active Comparator Phase, UTI was the most common SAE (all causality), reported for 1 subject each in the fesoterodine 4 mg and oxybutynin treatment arms. All other preferred terms (PTs) were each reported for only 1 subject.

  Among subjects who received at least 1 dose of fesoterodine in both the Active Comparator and Safety Extension Phases of Cohort 1, the incidence of SAEs (all causality) was low. All PTs were each reported for only 1 subject.

  For Cohort 2 during the Efficacy Phase, UTI was the most common SAE (all causality), reported for 1 subject in each treatment arm. All other PTs were each reported for only 1 subject.

  For Cohort 2 during the overall study, UTI was the most common SAE (all causality), reported for 1 subject in each treatment arm. All other PTs were each reported for only 1 subject.

  No treatment-related SAEs were reported during the study.

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- **Clinical Laboratory Evaluations**

  While there were individual cases that exceeded the normal range for individual laboratory parameters, there were no trends in occurrences of markedly abnormal laboratory findings during the Active Comparator or Safety Extension Phases of Cohort 1.

  While there were individual cases that exceeded the normal range for individual laboratory parameters, there were no trends in occurrences of markedly abnormal laboratory findings during the Efficacy or Safety Extension Phases of Cohort 2.

- **Vital Signs**

  For Cohort 1, no clinically relevant changes from baseline were observed for vital sign parameters in any of the treatments arms at the time points assessed. Increases from baseline in mean pulse rate were observed in the fesoterodine treatment arms, with the highest mean increase being 10.41 bpm at Week 4 of the Active Comparator Phase in the fesoterodine 8 mg treatment arm, but by Week 24 this had trended downwards to a mean increase of 6.54 bpm with a mean increase in the fesoterodine 4 mg arm of only 1.80 bpm. A mild TEAE of Heart rate increased was reported for 1 subject in the fesoterodine 8 mg arm. The TEAE was considered related to study treatment by the investigator, and the subject completed the study.

  For Cohort 2, no clinically relevant changes from baseline were observed for vital sign parameters in the fesoterodine 2 or 4 mg BIC arms at the time points assessed. Increases from baseline in mean pulse rate were observed in both fesoterodine treatment arms at Week 4 in the Efficacy Phase with the highest mean increase being 5.36 bpm in the fesoterodine 4 mg BIC arm, but by Week 24 there was no increase in mean pulse rate in the fesoterodine 2 mg BIC arm and only a mean increase of 4.86 bpm in the fesoterodine 4 mg BIC arm. A mild TEAE of Heart rate increased was reported for 1 subject in the fesoterodine 4 mg BIC arm. The TEAE was considered not related to study treatment by the investigator, and the subject completed the study. A mild TEAE of Tachycardia that was considered related to study treatment by the investigator was reported for 1 subject in the fesoterodine 2 mg BIC arm. The subject discontinued study drug and discontinued from the study due to the TEAE.

- **Physical Examination**

  For Cohort 1, there was no clinically relevant difference in the incidence of changes from baseline to Week 12 or Week 24 in physical examination findings between the treatment arms.

  For Cohort 2, there was no clinically relevant difference in the incidence of changes from baseline to Week 12 or Week 24 in physical examination findings between the fesoterodine 2 and 4 mg BIC arms.

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- **Visual Acuity and Accommodation**

  For Cohort 1, there were no clinically relevant changes from baseline to Week 12 or Week 24 in visual accommodation or visual acuity in either eye, for any of the treatment arms.

  For Cohort 2, there were no clinically relevant changes from baseline to Week 12 or Week 24 in visual accommodation or visual acuity in either eye, for either treatment arm.

- **Cognitive Function**

  For Cohort 1, there were no clinically relevant changes from baseline to Week 12 or Week 24 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 any of the treatment arms. There were no clinically relevant changes from baseline to Week 12 or Week 24 in GPT results in either the dominant or non-dominant hand for any of the treatment arms.

  For Cohort 2, there were no clinically relevant changes from baseline to Week 12 or Week 24 in the T score or total score of any CBCL assessments for either treatment arm. There were no clinically relevant changes from baseline to Week 12 or Week 24 in GPT results in either the dominant or non-dominant hand for either treatment arm.

- **Post-Void Residual Volume**

  For Cohort 1, there were no clinically relevant changes from baseline to Week 12 or Week 24 in PVR volume for any of the treatment arms.

  For Cohort 2, there were no clinically relevant changes from baseline to Week 12 or Week 24 in PVR volume for either treatment arm.

  PVR volume was only assessed for subjects not performing clean intermittent catheterization, resulting in small sample sizes. Therefore, it is not possible to draw any meaningful conclusions about the changes from baseline in PVR volume in this study.

Conclusions:

Efficacy

Cohort 1

- Treatment with fesoterodine 4 and 8 mg tablets resulted in significant improvements from baseline to Week 12 in the primary efficacy endpoint, maximum cystometric bladder capacity, for pediatric subjects with NDO aged 6 to 17 years weighing >25 kg, with

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numerically higher changes from baseline for fesoterodine 8 mg than for fesoterodine 4 mg.

- The improvement from baseline in the primary efficacy endpoint observed for fesoterodine 8 mg was of comparable magnitude to that of oxybutynin.

- Of the 11 secondary efficacy endpoints that were formally analyzed, 5 endpoints demonstrated significant improvements from baseline following treatment with fesoterodine 4 and 8 mg, whereas 7 demonstrated significant improvements from baseline following treatment with oxybutynin.

Cohort 2

- Treatment with fesoterodine 2 and 4 mg BIC resulted in improvements from baseline to Week 12 in the primary efficacy endpoint, maximum cystometric bladder capacity, for pediatric subjects with NDO aged 6 to 17 years weighing ≤25 kg, with numerically higher changes from baseline for fesoterodine 4 mg BIC than for fesoterodine 2 mg BIC.

- Of the 11 secondary efficacy endpoints that were formally analyzed, 5 endpoints demonstrated improvements from baseline following treatment with fesoterodine 4 mg BIC.

- Improvements from baseline were not demonstrated for any of the secondary efficacy endpoints following treatment with fesoterodine 2 mg BIC.

Safety

Cohort 1

- Treatment with fesoterodine 4 and 8 mg once daily for 12 weeks and for up to 24 weeks was well tolerated in pediatric subjects with NDO aged 6 to 17 years weighing >25 kg.

- There were no treatment-related SAEs and no deaths. Treatment-related TEAEs were mostly of mild to moderate severity.

- During the overall study for Cohort 1, the Infections and infestations system organ class (SOC) was the body system with the highest incidence of TEAEs. The most frequently observed infections were upper respiratory tract infections of a nature commonly seen in children or UTIs to which children with NDO are susceptible. The majority of reported infections were considered not to be related to study treatment by the investigators.

- During the Active Comparator Phase and the overall study, the most common treatment-related TEAEs were gastrointestinal disorders of Dry mouth, Constipation, Diarrhea, and Abdominal pain, which are consistent with the known safety profile of antimuscarinic agents when administered to adults.

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- During the Active Comparator Phase, the incidence of Dry mouth was significantly higher in the oxybutynin arm than in the fesoterodine 4 and 8 mg arms. There was no significant difference in the incidence of any other reported Tier-1 TEAE between the oxybutynin arm and the fesoterodine arms. Overall, there was a numerically higher incidence of antimuscarinic effects in the oxybutynin arm compared with the fesoterodine arms.

- During the overall study, there were no TEAEs of seizures or somnolence and no clinically relevant changes were observed in cognitive function or behavior measured by CBCL and GPT.

- No clinically relevant changes were observed for visual acuity and accommodation, PVR volume, vital signs, physical examinations, weight, or clinical laboratory tests for Cohort 1 during the overall study.

Cohort 2

- Treatment with fesoterodine 2 and 4 mg BIC once daily for 12 weeks and for up to 24 weeks was well tolerated in pediatric subjects with NDO aged 6 to 17 years weighing ≤25 kg.

- There were no treatment-related SAEs and no deaths. Treatment-related TEAEs were of mild to moderate severity.

- During the Efficacy Phase and the overall study for Cohort 2, the Infections and infestations SOC was the body system with the highest incidence of TEAEs. The most frequently observed infections were upper respiratory tract infections of a nature commonly seen in children or UTIs to which children with NDO are susceptible. All reported infections were considered not to be related to study treatment by the investigators.

- In the study overall, the highest incidence of treatment-related TEAEs by body system occurred in the Gastrointestinal disorders SOC, which is consistent with the known safety profile of antimuscarinic agents when administered to adults.

- The only central nervous system TEAEs reported were headache and dizziness, which are both consistent with the known safety profile in adults. There were no TEAEs of seizures or somnolence, and no clinically relevant changes were observed in cognitive function or behavior measured by CBCL or GPT.

- No clinically relevant changes were observed for visual acuity and accommodation, PVR volume, vital signs, physical examinations, weight, or clinical laboratory tests for Cohort 2 during the overall study.

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Pharmacokinetics

- The mean (%RSE) values of 5-HMT CL/F, Vd/F and Ka in pediatric subjects with NDO aged 6 to 17 years are estimated to be 71.6 (6.7) L/hour, 68.1 (29.7) L, and 0.0897 (5.99)/hour, respectively.

- Within each cohort of pediatric subjects with NDO aged 6 to 17 years, the individual and mean plasma 5-HMT concentrations following administration of fesoterodine 4 and 8 mg tablets once daily (Cohort 1) and those following fesoterodine 2 and 4 mg BIC formulation once daily (Cohort 2) increased in a proportion similar to the increment in doses.