Protocol A0221047

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)

Statistical Analysis Plan (SAP)

Version: Version 2.0

Author: PPD (All versions, GBDM)

Date: 25 February 2020

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[redacted]

LIST OF TABLES

[redacted]

1. AMENDMENTS FROM PREVIOUS VERSION(S)

The table below outlines the changes that have been made to this SAP.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment (PA)	Rationale	Specific Changes
Use whole numbers starting with 1 for original SAP. *Ensure the date matches the final approval date.*	*Specify if and what amendment is associated: Terms should be: N/A, Original, or Amendment number;* *Include date of protocol.*	*Specify the primary reason for the changes – Specific reasons to use can be:* • *Regulatory input.* • *DMC request.* • *External environment (competitor information).* • *Blinded data review.* • *Clarification or completion of prior version (eg, when a section was initially TBD).*	*Summarize the changes; use bullets if needed. Be specific about which sections major changes impact. Minor clarifications can be grouped together.*
1 25 Jan 2012	Original 03 Aug 2010	N/A	N/A
1.1 12 Feb 2013	PA 4 02 Oct 2012	Updates prior to first EDMC meeting to clarify some of the safety analyses following further discussions with programming	• Included information on how missing days and months for Dates of Birth will be imputed. • The AE tables for the safety extension phase will have two additional treatment groups: Feso 4mg>Feso 4mg and Feso 8mg>Feso 8mg. • The treatment groups to be used for each of the safety analysis sets have been specified. • Additional detail added about which PVR results to use and the conversion to LogMAR values for visual acuity. • Additional pulse rate cut-offs added.

[redacted]

			• Additional minor clarifications to align with the updated DMB02-GSOP-RF02 Statistical Analysis Plan Template (SAP), effective 31-Jan-2013
1.2 14 Apr 2014	PA 5 3 Mar 2014	Protocol amended to include lighter weight cohort (Cohort 2 - subjects ≤25kg), originally planned to be studied under a separate protocol (A0221074).	• The SAP has been amended to describe the analyses for Cohort 2. The intention is to analyse and summarize each cohort separately, therefore additional sections have been added into the SAP specifically to describe the Cohort 2 analyses and summaries.
2.0 25 Feb 2020	N/A	Prior to DB Release	• Removal of figures and listings that have been removed from the List of Tables (LOT) as part of the TLF reduction exercise. The data presented in the figures that have been removed are presented in tables. • Exploratory analyses and subgroup figures removed as these won't be included in the CSR. Some have been replaced by descriptive subgroup summary tables instead. • As some subjects will only record micturitions in their bladder diary (if they are not catheterizing) and some will only record catheterizations (if they only catheterize), these two endpoints will only be calculated for subjects with >0 episodes at baseline. • Section 8.2.5 (Other Adverse Event Reporting) has been updated to clarify that the lag period is only applied if a subject discontinues study medication in the Active Comparator/ Efficacy Phase (otherwise, for subjects who continue into the Safety Extension AEs could be counted twice). • Other minor updates to ensure SAP is aligned with how results are being presented in tables, figures and listings.

The study is ongoing, and unblinded data from the study have been reviewed by an External Data Monitoring Committee; however that review has not influenced any of the changes documented in this amendment.

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicised***.

- ***Drug Development rationale***

Antimuscarinic drugs are the cornerstone of pharmacotherapy in the pediatric neurogenic bladder population, and have been shown to improve intravesicular pressure, and decrease symptoms. Four antimuscarinic drugs (oxybutynin, trospium chloride, tolterodine and darifenacin) have documented results in the pediatric neurogenic bladder population - Kennelly & DeVoe, 2008 [1]. Of these, only oxybutynin is widely approved for use in children, and is available as a once a day extended release tablet, as well as an immediate release tablet. Although effective, oxybutynin use has been limited by a side effect profile which may have particular relevance in the pediatric population where development (eg, physical, cognitive, psychosocial) is still ongoing.

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

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

Other treatments such as alpha blockers, anxiolytics, tricyclic antidepressants, intravesical oxybutynin, botulinum-A toxin, electrical stimulation and biofeedback, may also be used - Coward & Saleem, 2001 [2], although safety and efficacy have not been reliably demonstrated.

- ***Study rationale***

The primary purpose of this study is to evaluate the safety and efficacy of fesoterodine 4 mg and 8 mg PR (prolonged release) *once daily* (body weight >25 Kg) and fesoterodine 2 mg and 4 mg BIC (beads-in-capsule) once daily (body weight ≤25 Kg) *in pediatric NDO subjects aged between 6-17 years. Additionally, the safety and efficacy of oxybutynin extended release (XL) will be evaluated in subjects >25 kg only.*

Sparse PK samples will also be obtained to determine the steady-state population pharmacokinetics of 5- hydroxymethyltolterodine (5-HMT) following fesoterodine treatment in pediatric NDO subjects.

[redacted]

The study will enroll two weight cohorts as follows:

- *Cohort 1*

  For subjects >25 kg, following 12 weeks of treatment with either fesoterodine 4 mg, 8 mg PR (adult tablet formulation) *or oxybutynin XL in an active comparator phase, subjects will then enter a safety extension phase* and continue to receive *4 mg or 8 mg of fesoterodine PR for an additional 12 weeks.* Subjects that received oxybutynin in the active comparator phase will receive 4 mg or 8 mg fesoterodine PR for the 12 weeks safety extension phase*. This cohort will include subjects 25.1 kg and above.*

- *Cohort 2*

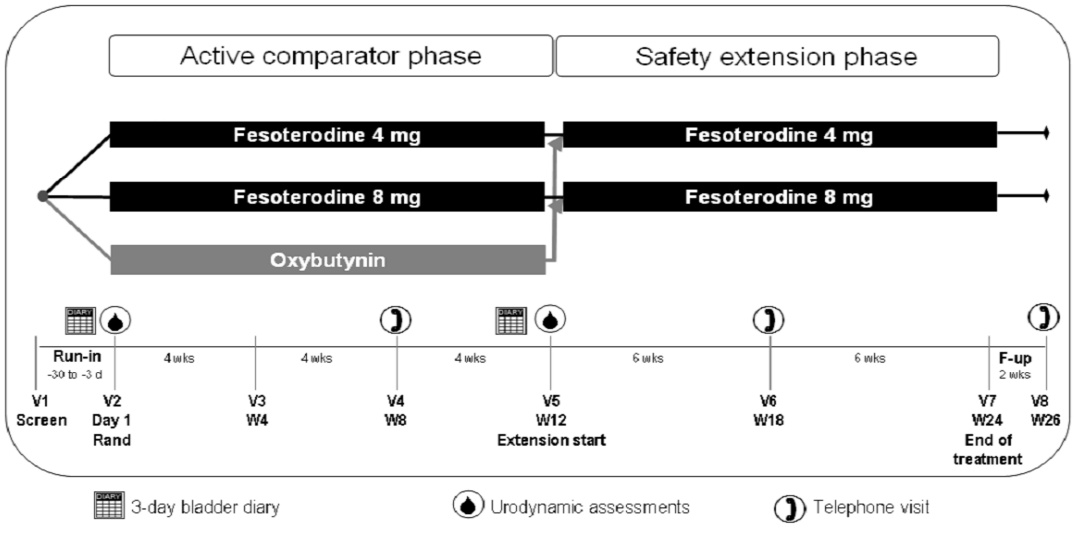
  For subjects ≤25 kg, following 12 weeks of treatment with either fesoterodine 2 mg or *4 mg BIC (beads-in-capsule formulation) in an efficacy phase, subjects will then enter a safety extension phase receiving the same dose of fesoterodine for an additional 12 weeks. NB. This cohort will include subjects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

2.1. Study Design

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

Cohort 1 (Subjects >25 kg)

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



[redacted]

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

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

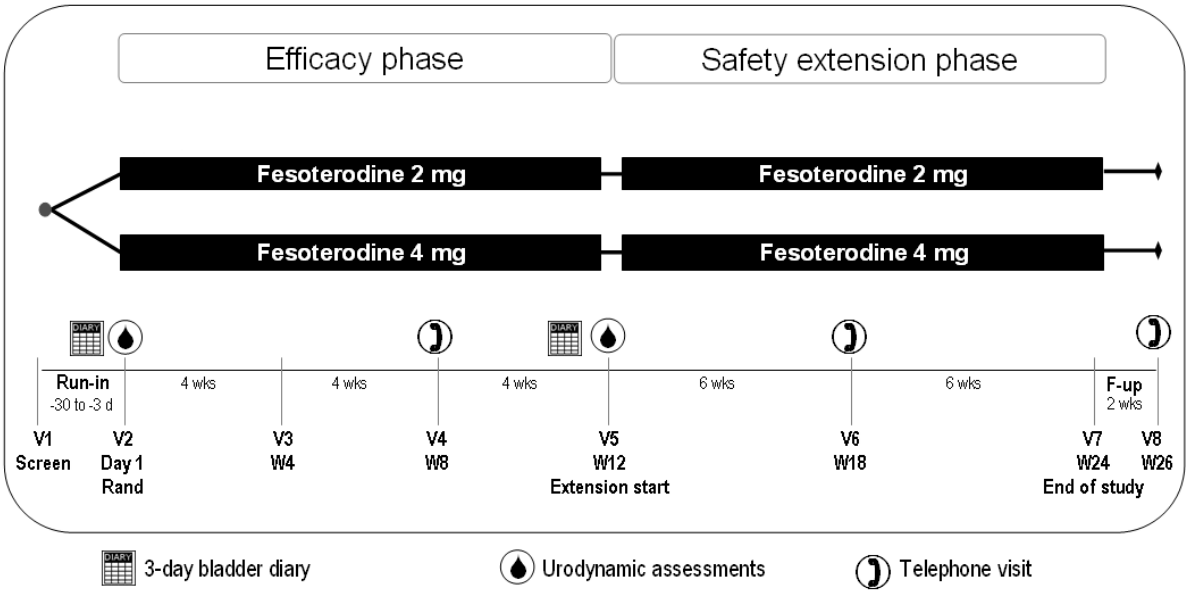
There is a variable screening period (minimum 3 days) prior to the baseline visit, the duration of which is principally determined by the prior medication subjects may need to washout. At baseline, subjects will be randomized to one of three arms: 4 mg or 8 mg/day of fesoterodine PR or oxybutynin XL.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

After 12 weeks (or earlier if appropriate), subjects in the oxybutynin arm of the study will be allocated by the investigator to fesoterodine PR at either 4 mg or 8 mg/day. Subjects in the fesoterodine arms will remain on the same dose they were randomized to during the 12 week safety extension phase.

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

[redacted]

Cohort 2 (Subjects ≤25 kg)



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

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

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

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

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

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

[redacted]

2.2. Study Objectives

The primary objectives of this study are:

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

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

The secondary objectives of this study are to:

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

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

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

- *determine the steady-state population pharmacokinetics of 5-HMT following treatment with two doses of fesoterodine 2 mg and 4 mg* BIC *treatment once daily in pediatric NDO subjects with weight ≤25 kg.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

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

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

[redacted]

This study will use an External Data Monitoring Committee (EDMC) for the purpose of protecting the safety of patients by regular independent assessment of risk/benefit during the conduct of the study (for each cohort separately as well as combined).

The EDMC will meet at specified intervals during the study to assess its progress including the safety data and/or critical efficacy endpoints. Safety data will include assessment of adverse events, vision testing, CBCL/GPT assessments, vital signs including heart rate, incidence of urinary tract infection (as evidenced by urinalysis, urine microscopy and culture), clinical laboratory evaluations in the context of age-appropriate norms, with particular reference to liver function tests and renal chemistry, and post-void residual volume (PVR) in subjects not performing CIC, or with >1 urinary tract infection (UTI) during the study.

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

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

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

The final analysis will be performed following official database release, once all subjects have completed the whole study.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The following hypotheses are applicable only to the analyses of the heavier (>25 Kg) Cohort 1, as there is 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.

[redacted]

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

Sample Size Determination

Cohort 1 (>25 kg)

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

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

Cohort 2 (≤25 kg)

A sample size of approximately 25 evaluable subjects per arm will provide a 2-sided 95% confidence interval for the change from baseline in maximum cystometric capacity (MCC) of approximately ± 55 mL around the point estimate for the mean, with 80% coverage probability. This assumes a standard deviation of 120 mL. This is based on results observed from the two highest dose periods (each 4 weeks) in previous tolterodine neurogenic bladder studies 583E-URO-0581-001, 583E-URO-0581-002 and 583-URO-0581-003, as well as published data from studies of oral oxybutynin in neurogenic OAB patients. It is planned that a sufficient number of subjects will be randomized into this cohort to ensure a total of approximately 50 subjects (25 evaluable subjects per arm) are evaluable at Week 12.

4.2. Statistical Decision Rules

Changes from baseline in Cohort 1 will be tested at the α=0.05 level, and 95% Confidence Intervals will be estimated for Cohort 2.

5. ANALYSIS SETS

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

[redacted]

5.1. Full Analysis Set

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

This is to utilize as much data as possible from any subjects with urodynamic data available for analysis and will not exclude subjects with only baseline data available.

5.2. Per Protocol Analysis Set

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

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

5.2.1. Deviations assessed prior to randomization

Violation of a major inclusion/exclusion criterion prior to randomisation would be considered a protocol violation. The criteria and determination of protocol violation/deviation will be determined by Pfizer prior to database lock.

5.2.2. Deviations assessed post-randomization

Violation of a major inclusion/exclusion criterion post randomisation would be considered a protocol violation, for example:

- Initiation of a prohibited concomitant medication.
- Study drug compliance <80% or >120%.
- Incomplete primary endpoint data at week 12.

The criteria and determination of protocol violation/deviation will be determined by Pfizer prior to database lock.

5.3. Safety Analysis Set

There will be three safety analysis sets for Cohort 1 (to be utilized for AEs and duration of treatment summaries):

- Active Comparator Phase safety set: all subjects who received at least one dose of study medication during the active comparator phase. The following treatment assignments will be used for this analysis set:
  - Fesoterodine 4mg PR;
  - Fesoterodine 8mg PR;
  - Oxybutynin.

[redacted]

- Safety Extension Phase safety set: all subjects who received at least one dose of study medication during the safety extension phase. The following treatment assignments will be used for this analysis set:
  - Oxybutynin -> Fesoterodine 4mg PR;
  - Oxybutynin -> Fesoterodine 8mg PR;
  - Fesoterodine 4mg PR -> Fesoterodine 4mg PR;
  - Fesoterodine 8mg PR -> Fesoterodine 8mg PR.
- Overall study safety set: subjects who were randomized to fesoterodine during the active comparator phase and received at least one dose of study medication during both phases of the study:
  - Fesoterodine 4mg PR (24 weeks);
  - Fesoterodine 8mg PR (24 weeks).
- For all other Safety tables, the Safety Analysis Set will just consist of all subjects who received at least one dose of study medication at any time during the study (ie, in either phase). The following treatment assignments should be used for this:
  - Oxybutynin -> Fesoterodine 4mg PR;
  - Oxybutynin -> Fesoterodine 8mg PR;
  - Oxybutynin;
  - Fesoterodine 4mg PR -> Fesoterodine 4mg PR;
  - Fesoterodine 8mg PR -> Fesoterodine 8mg PR.

NB: All randomized subjects will be used for summarizing discontinuations in the Active Comparator Phase and overall, and for data collected at baseline.

There will be three safety analysis sets for Cohort 2 (to be utilized for AEs and duration of treatment summaries):

- Efficacy Phase safety set: all subjects who received at least one dose of study medication during the efficacy phase. The following treatment assignments will be used for this analysis set:
  - Fesoterodine 2mg BIC;
  - Fesoterodine 4mg BIC.
- Safety Extension Phase safety set: all subjects who received at least one dose of study medication during the safety extension phase. The following treatment assignments will be used for this analysis set:
  - Fesoterodine 2mg BIC -> Fesoterodine 2mg BIC;
  - Fesoterodine 4mg BIC -> Fesoterodine 4mg BIC.

[redacted]

- For all other Safety tables, the Safety Analysis Set will just consist of all subjects who received at least one dose of study medication at any time during the study (ie, in either phase). The following treatment assignments should be used for this:
  - Fesoterodine 2mg BIC -> Fesoterodine 2mg BIC;
  - Fesoterodine 4mg BIC -> Fesoterodine 4mg BIC.

NB: All randomized subjects will be used for summarizing discontinuations in the Efficacy Phase and overall, and for data collected at baseline.

5.4. Pharmacokinetic (PK) Analysis Set

The following PK Analysis Sets will be determined for each cohort separately.

Concentration Analysis Set

The PK concentration population is defined as all subjects randomized and treated who have at least 1 concentration during the study.

Parameter Analysis Set

The PK parameter analysis population is defined as all subjects randomized and treated who have at least 1 of the PK parameters of primary interest during the study.

5.5. Treatment Misallocations

Subjects who are randomized but never treated will not be included in either safety or efficacy analyses. For a randomized subject who took the incorrect treatment, he/she will be reported under the randomized treatment group for all efficacy analyses, but will be reported under the treatment they actually received for all safety analyses.

5.6. Protocol Deviations

5.6.1. Deviations assessed prior to randomization

See Section 5.2.1

5.6.2. Deviations assessed post-randomization

See Section 5.2.2

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

6.1.1. Primary Endpoint

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

[redacted]

6.1.2. Secondary Endpoints

- Detrusor pressure at maximum bladder capacity;
- Presence of involuntary detrusor contractions (IDC);
- Bladder volume at first IDC;
- Bladder compliance.

Defined as Δvolume/Δpressure during that change in bladder volume.

- Mean number of micturitions per 24 hours.

The mean number of micturitions per 24 hours will be calculated as the total number of micturitions divided by the total number of diary days collected at that assessment. This endpoint will only be calculated for subjects with >0 episodes at baseline.

- Mean number of catheterizations per 24 hours.

The mean number of catheterizations per 24 hours will be calculated as the total number of catheterizations divided by the total number of diary days collected at that assessment.* This endpoint will only be calculated for subjects with >0 episodes at baseline.

*Note: The number of diary days collected at that assessment is the number of calendar days that the diary has been completed on (even if this may not be a full 24 hour period). For example, if a diary has been completed for 3 complete days and the morning of the fourth day, this would count as 4 days. This derivation is the same for all the diary endpoints listed ‘per 24 hours’.

- Mean number of micturitions and catheterizations combined per 24 hours.

The mean number of micturitions and catheterizations combined per 24 hours will be calculated as the total number of micturitions and catheterizations combined divided by the total number of diary days collected at that assessment.

- Mean number of incontinence episodes per 24 hours.

The mean number of incontinence episodes per 24 hours will be calculated as the total number of incontinence episodes divided by the total number of diary days collected at that assessment. This endpoint will only be calculated for subjects with >0 episodes at baseline.

- Mean urgency episodes per 24 hours if applicable (only for sensate subjects, ie, able to physically experience the sensation of urgency - as indicated in CRF).

[redacted]

The mean number of urgency episodes per 24 hours will be calculated as the total number of urgency episodes divided by the total number of diary days collected at that assessment. Urgency episodes are defined as Urgency marked as 'yes' in the diary. This endpoint will only be calculated for subjects with >0 episodes at baseline.

- Mean volume voided per micturition.

The mean voided volume per micturition will be calculated as sum of voided volume divided by the total number of micturition episodes with a recorded voided volume greater than 0, regardless of the number of available diary days at that assessment. Note: missing or zero voided volume will not be included in this calculation

- Mean volume per catheterization.

The mean volume per catheterization will be calculated as sum of voided volume divided by the total number of catheterization volume greater than 0, regardless of the number of available diary days at that assessment. Note: missing or zero voided volume will not be included in this calculation

- Mean volume voided per micturition or catheterization.

The mean voided volume per micturition or catheterization will be calculated as sum of voided volume divided by the total number of micturition episodes with a recorded voided volume greater than 0, regardless of the number of available diary days at that assessment. Note: missing or zero voided volume will not be included in this calculation

6.2. Safety Endpoints

- Adverse events, including monitoring of targeted events including, but not limited to:
  - Anticholinergic effects such as dry mouth, dry eyes and constipation.
  - CNS effects such as behavioral changes (eg, aggression), decreased cognitive function, headache, seizures, somnolence.
  - Visual effects such as accommodation disorder, blurred vision, and amblyopia.
- Visual acuity and accommodation tests.
- Cognitive function by the Child Behavior Checklist and Grooved Pegboard Test.
- Vital Signs, including heart rate in the context of age-appropriate norms.

- Urinary Tract Infection, as evidenced by urinalysis, urine microscopy, culture and sensitivity.
- Clinical Laboratory Evaluations in the context of age-appropriate norms, with particular reference to liver function tests and renal chemistry.
- Post-void residual volume (PVR) in subjects not performing CIC, or with >1 urinary tract infection (UTI) during the study.
- Physical Examination and weight.

6.2.1. Adverse Events

Adverse event information will be collected for all subjects. Information that will be collected includes: nature of event, whether event was serious; date of onset; date of cessation or event continuing; severity of event; relationship of event to study drug; action taken regarding study drug due to the event; clinical outcome of event.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (See Section 8.2.5).

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA PT is defined as a tier-2 event if there are at least 4 subjects in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events

Visual acuity and accommodation tests

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

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

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

6.2.2. Vital Signs

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

[redacted]

resolves. The measured results will be assessed in the context of age appropriate norms.

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

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

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

6.2.3. Physical Exam

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

- *General appearance (including weight).*
- *Skin.*
- *HEENT (head, eyes, ears, nose, throat, visual acuity and accommodation).*
- *Respiratory.*
- *Cardiovascular.*
- *Gastrointestinal.*
- *Musculoskeletal.*
- *Neurourological.*

Additional physical assessments will be performed as necessary to evaluate the subject. Any clinically significant negative changes from the entry examination will be recorded as adverse events.

6.2.4. Weight Measurements

Weight will be recorded at Screening and used to assess eligibility and for stratification purposes. Subsequently weight will be recorded at Visit 3, Visit 5, and Visit 7. All weight measurements should be standardized using the same equipment and measuring technique for an individual subject. Any clinically significant change in weight should be reported as an adverse event.

[redacted]

6.2.5. Electrocardiogram

Scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. A single 12-lead ECG will be obtained on all subjects at screening.

6.2.6. Clinical Laboratory Evaluation

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

Safety Laboratory

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

[a] Urine microscopy, culture and sensitivity to be performed in the event of the presence of symptoms (eg, fever, flank pain), positive leucocytes and/or nitrites on urinalysis, or if the subject has a documented history of vesicoureteral reflux (VUR).
Subjects who are found to have an active UTI during screening as defined in exclusion criterion 12 may continue screening activities on resolution of symptoms or treatment of the UTI to the satisfaction of the treating physician.
[b] Females of childbearing potential only (≥9 years old or have experienced menarche, whichever is earlier). Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
[c]When indicated, the investigator may request calculation of an estimated GFR using the Schwartz equation GFR = (k x H)/Cr where k = constant, H = Height (length) and Cr = Creatinine. In this case, the laboratory will need to be provided with the subject's height in cm.
[d] *PG and PK samples are for fesoterodine group subjects only.*

6.2.7. Childhood Behavior Checklist (CBCL)

The CBCL is a questionnaire by which a child's problem behaviors and competencies can be assessed. This instrument can either be self-administered or administered through an interview. The CBCL can also be used to measure a child's change in behavior over time or following a treatment. The first section of this questionnaire consists of 20 competence items and the second section consists of 120 items on behavior or emotional problems. For the purpose of this trial, subjects will be asked to complete 113 items on behavior and emotional problems.

[redacted]

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

6.2.8. Grooved Pegboard Test (GPT)

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

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

6.3. Pharmacokinetic Evaluations

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

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

Population pharmacokinetic analyses will be conducted via nonlinear mixed-effects modeling with the NONMEM® software, Version VI (ICON Development Solutions, Ellicott City, MD). Model-based parameter estimates for absorption rate constant (Ka), apparent oral clearance (CL/F) and volumes of distribution (Vd) will be determined to predict the area under the curve (AUC), maximum concentration (C_{max}), time to reach C_{max} (T_{max}) and half-life of 5-HMT in patients randomized to fesoterodine treatment. Possible influences of patient covariates (eg, age, body weight, gender, CYP2D6 metabolizer status etc.) on 5-HMT exposure will be assessed.

6.4. Covariates

The baseline observation for the endpoint being analyzed will be used as a continuous covariate in any ANCOVA analyses.

[redacted]

Baseline weight will be used as a continuous endpoint in any ANCOVA analyses.

The following subgroups will be assessed for the primary endpoint:
Age: Ages ≥6-9, ≥10-12, ≥13-17
Weight: Cohort 1: ≤50 kg, >50 kg, Cohort 2: ≤20 kg, >20 kg
Gender: Male, Female
Region: Cohort 1: North America, Europe, Asia, Cohort 2: North America and Europe, Asia
Type of Underlying Disease: Congenital, Acquired, Unknown
Race: White, Asian, Black, Other (where Other includes: American Indian or Alaska Native, Native Hawaiian or other Pacific Islander)
Ethnicity: Hispanic/Latino, Not Hispanic/Latino

Underlying disease will be categorised as 'congenital' or 'acquired' and will be determined through manual review of medical history listings (by the clinician) for Cohort 1. If this is unable to be determined, this will be categorized as 'Unknown'. For Cohort 2 the answer to the question "Underlying Cause of Primary Diagnosis" on the Primary Diagnosis eCRF page will be utilized, for which the responses are 'Congenital' or 'Acquired'.

7. HANDLING OF MISSING VALUES

Missing visits

For the PPAS analysis no imputation techniques for missing data will be employed. For the FAS analysis a combination of Baseline Observation Carried Forward (BOCF) and a Last Observation Carried Forward (LOCF) algorithm will be used for missing data. For example, where a subject has no post-baseline observation then the baseline observation will be carried forward and used for Week 12 analyses; if a subject withdraws early then their termination visit will be carried forward (note this will be labelled as 'Week 12' in the dataset).

Diary Data

For the analysis involving diaries, time-points will be defined as non-overlapping periods. See Appendix B for definition of time intervals. Missing daily micturition data will be estimated as the following:

1. If one out of three days is missing, the mean of the remaining days will be used to impute the micturition data for the missing day/days.

2. The LOCF/BOCF imputations will be carried out for time-intervals with missing diary data. For intervals where less than two days of diary data are available, the previous available 3-day post-baseline interval values will then be carried forward.

[redacted]

Micturition volume is collected on one day only therefore if it is missing at a visit the previous visit's data will be carried forward.

Note: In subjects who withdraw after a minimum of 2 weeks of treatment, attempts should be made to perform a urodynamic assessment, provided that they have not missed any doses in the three days previous to the visit.

Plasma concentrations

Concentrations below the limit of quantification

In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

Missing concentrations values

In summary tables, statistics will be calculated having set concentrations to missing if the following case is true:

- A concentration has been collected as ND (ie not done) or NS (ie no sample).

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

Date of Birth

In the case where the whole Date of Birth is not entered, the last day of the month will be used to impute the missing day, and 31st December will be used if both the day and month are missing.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical METHODS

Treatments will be labeled as follows in all the data summaries:

Cohort 1:
Fesoterodine 4 mg PR
Fesoterodine 8 mg PR
Oxybutynin

Cohort 2:
Fesoterodine 2 mg BIC
Fesoterodine 4 mg BIC

[redacted]

8.1.1. Analysis of Continuous Data

Where data is to be summarized using descriptive statistics the following will be presented: n, mean, standard deviation, median, minimum, and maximum.

8.1.2. Analysis of Binary Data

Binary endpoints will be presented using cell counts and proportions for each response category. For summaries of change from baseline the tables will be presented as a cross tabulation with baseline visit along the side and week 12 results along the top.

8.2. Statistical Analyses

8.2.1. Cohort 1: Primary Analysis

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

All endpoints will also be summarized descriptively for each treatment group, by timepoint as for a continuous endpoint. Should any of the assumptions of the analysis methods not be adequately met, alternative procedures will be used and fully documented.

The following primary comparisons of interest will be assessed:

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

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

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

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

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

[redacted]

Forest plots presenting the mean and 95% confidence intervals for the change from baseline for Fesoterodine 4mg PR, Fesoterodine 8mg PR and Oxybutynin will be produced. In addition the mean difference and its associated 95% confidence interval between change from baseline for Fesoterodine 4 mg PR vs. Oxybutynin and Fesoterodine 8 mg PR vs. Oxybutynin will be also presented in a separate plot.

The primary analysis will be based on the Full Analysis Set (FAS). The secondary analysis set will be the Per Protocol Analysis Set (PPAS).

Data from the active comparator phase of the study may be summarized, analyzed and reported after all subjects have either completed or withdrawn prior to the Week 12 visit or from both phases after all subjects in Cohort 1 have either completed or withdrawn prior to the end of the study (ie, prior to formal completion of the whole study for both cohorts). If performed, the results of these analyses will be assessed by the EDMC and will be available to limited members of the study team as a management tool in order to aid decision making, and may also be shared with regulators in order to facilitate timely discussion of the overall program; they will not be used to stop or modify the design of the study.

Descriptive subgroup analyses of the change from baseline to Week 12 in the primary endpoint will be produced by age group, weight group, race, ethnicity, gender, region and underlying type of disease.

8.2.2. Cohort 2: Primary Analysis

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

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

The following primary comparisons of interest will be assessed:

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

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

[redacted]

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

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

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

Descriptive subgroup analyses of the change from baseline to Week 12 in the primary endpoint will be produced by age group, weight group, race, ethnicity, gender, region and underlying type of disease.

8.2.3. Secondary Analyses

All secondary endpoints will be analysed as for the primary analyses as defined for each respective cohort using the appropriate full analysis set. A further analysis of the key secondary endpoints of Bladder compliance and IDC will use the per protocol analysis set.

The presence of IDC will be analyzed as for discrete endpoints.

8.2.4. Other Endpoints

The following analyses will be carried out for subjects randomised to Fesoterodine only (for each cohort separately).

Pharmacokinetic Concentrations

Plasma concentrations of 5-HMT will be listed and summarized for subjects in the PK analysis set, where missing and BLQ values will be handled as detailed in Section 7.

Presentations will include:

- a listing of all concentrations sorted by visit, dose, subject ID and nominal time postdose. The listing of concentrations will include the actual times.

- if data permit, a summary of concentrations by visit, dose and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, minimum, maximum, coefficient of variation (cv) and the number of concentrations above the lower limit of quantification.

[redacted]

Pharmacokinetic Parameters

Model based PK parameters (from POP PK analysis) will be described in a separate plan.

8.2.5. Safety Analyses

Tables of safety and demographic data, including adverse events and medical history in this report will be reported in accordance with current Pfizer standards, and will be presented separately for each cohort. Safety summaries of both cohorts combined may also be produced. Adverse events will be summarized by treatment group as specified for the Three Tier Adverse Event Reporting and for Other Adverse Event Reporting.

All other safety summaries will be summarised by the following treatment groups (as safety data will be captured throughout the Active Comparator/Efficacy and Safety Extension phases):

Cohort 1:
Oxybutynin -> Fesoterodine 4mg PR
Oxybutynin -> Fesoterodine 8mg PR
Oxybutynin (only)
Fesoterodine 4mg PR -> Fesoterodine 4mg PR
Fesoterodine 8mg PR -> Fesoterodine 8mg PR

Cohort 2:
Fesoterodine 2mg BIC -> Fesoterodine 2mg BIC
Fesoterodine 4mg BIC -> Fesoterodine 4mg BIC

Three Tier Adverse Event Reporting

The presentations described in this section will only concern treatment emergent adverse events which occurred during the active comparator/efficacy phases of this study for each cohort, and will be presented separately for each cohort. The active comparator/efficacy phase is defined as first dose to week 12 plus a lag time of 7 days.

Where presented, for Cohort 1, the treatment comparisons will be Fesoterodine 4mg vs. Oxybutynin and Fesoterodine 8mg vs. Oxybutynin. The risk difference will be calculated as Fesoterodine (4mg PR or 8mg PR) minus Oxybutynin. There will be no treatment comparisons presented for Cohort 2, as there is no active comparator for this cohort.

Adverse events will be presented in order of system organ class.

Tier 1 Adverse Event Reporting

Tier 1 summaries will only report those adverse events which have been identified as targeted medical events (TMEs) in the safety review plan.

[redacted]

The percentage of subjects experiencing a particular adverse event in each treatment group will be presented both in a table and graphically. The table will present the point estimate for the percentage of affected subjects, along with risk differences, their 95% confidence intervals and p-values, for Cohort 1 (fesoterodine 4mg PR or 8mg PR minus Oxybutynin). However for Cohort 2, only point estimates will be presented, as there is no active comparator for this cohort.

Graphical presentations will include the point estimate for the percentage of affected subjects, along with the risk differences and their 95% confidence intervals for Cohort 1, and point estimates only for Cohort 2.

Tier 2 Adverse Event Reporting

Tier 2 summaries will only report those adverse events which occurred to 4 or more subjects in any treatment group.

The percentage of subjects experiencing a particular adverse event in each treatment group will be presented both in a table and graphically. The table will present the point estimate for the percentage of affected subjects, along with the risk differences and their 95% confidence intervals, for Cohort 1. However for Cohort 2, only point estimates will be presented, as there is no active comparator for this cohort.

Graphical presentations will include the point estimate for the percentage of affected subjects, along with the risk differences and their 95% confidence intervals for Cohort 1, and point estimates only for Cohort 2.

Tier 3 Adverse Event Reporting

Tier 3 adverse events are events that are neither tier-1 nor tier-2 events, however these will not be summarized separately. All adverse events (Tier 1, 2 and 3 adverse events) will be presented together in table form only. The frequency and percentage of subjects will be presented by treatment group.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

Other Adverse Event Reporting

Adverse events will be reported separately for the active comparator phase, the safety extension phase and over the entire study. Summaries will be presented as follows:

[redacted]

For the Active Comparator/Efficacy Phase:

The active comparator/efficacy phase is defined as the first dose up to week 12 if the subject continues into the Safety Extension Phase. If a subject has discontinued early during the active comparator/efficacy phase, the reporting period for this phase will be up to their last dose of study medication plus the drug specific lag time. For Fesoterodine this will be 7 days, however for Oxybutynin (Cohort 1 only) this will be either 2 days or the time until first treatment of Fesoterodine in the safety extension phase, whichever is longer. The following treatment groups will be summarized.

Cohort 1:
Fesoterodine 4mg PR
Fesoterodine 8mg PR
Oxybutynin

Cohort 2:
Fesoterodine 2mg BIC
Fesoterodine 4mg BIC

For the Safety Extension Phase:

The safety extension phase is started after the first dose of fesoterodine in the safety extension phase is administered. Only adverse events that started or worsened in the Safety Extension phase would be counted as treatment emergent in this phase. Note that treatment emergent AEs will be defined as described in the Pfizer Data Standards for cross over studies. The following treatment groups will be summarized.

Cohort 1:
Oxybutynin -> Fesoterodine 4mg PR
Oxybutynin -> Fesoterodine 8mg PR
Fesoterodine 4mg PR -> Fesoterodine 4mg PR
Fesoterodine 8mg PR -> Fesoterodine 8mg PR

Cohort 2:
Fesoterodine 2mg BIC -> Fesoterodine 2mg BIC
Fesoterodine 4mg BIC -> Fesoterodine 4mg BIC

For the whole study (overall):

These presentations will only include subjects who were randomised to fesoterodine.

Cohort 1:
Fesoterodine 4mg PR (24 weeks)
Fesoterodine 8mg PR (24 weeks)

Cohort 2:
Fesoterodine 2mg BIC (24 weeks)
Fesoterodine 4mg BIC (24 weeks)

[redacted]

Plots displaying the point estimate for the percentage of subjects in each treatment group who experience adverse events of particular interest will be presented for the Safety Extension phase and for the study as a whole.

Vital Sign Reporting

For vital signs change from baseline will be summarized together with the number of subjects whose blood pressure and heart rate fall outside specified ranges. Furthermore, the number of subjects who decreases and increases in responses fall outside specified ranges will be summarized (for blood pressure only).

Endpoint	Cutoff
Systolic Blood Pressure SBP Increase from Baseline SBP Decrease from Baseline	<90 ≥30 ≥30
Diastolic Blood Pressure DBP Increase from Baseline DBP Decrease from Baseline	<50 ≥20 ≥20
Pulse	<40 or >120

At all visits, for replicates, the second PVR value should be reported. This should also be the smallest if done per protocol. This should be footnoted as follows: "Only the second PVR urine volume is reported in the summary tables in cases where a repeat PVR assessment is made".

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 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 Exam and Weight will be summarized by visit and changes from baseline at each visit using descriptive statistics.

For Visual Acuity, LogMAR units will be derived from the Snellen ratios recorded on the CRF, as shown in the table below. The decimal is the Snellen ratio (whether it is recorded in metres or feet) expressed as a decimal and LogMAR=Log_{10}(1/decimal) (recorded to 1 d.p.). Due to the limited space available in the CRF, the Snellen ratio '20/12.5' will be recorded as '20/13', however this should still be converted to a decimal value of 1.60 and a LogMAR value of -0.2 as shown in the table below. If the Snellen Visual Acuity has been recorded in any other format than those shown below, the appropriate conversion to decimal will be determined prior to database lock.

[redacted]

Table 3
Equivalent visual acuity measurements

Snellen visual acuity					
20 ft	6 m	4 m	Decimal	MAR[a]	LogMAR
20/640	6/192	4/128	0.03	32	1.5
20/500	6/152	4/100	0.04	25	1.4
20/400	6/120	4/80	0.05	20.0	1.3
20/320	6/96	4/63	0.063	16	1.2
20/250	6/76	4/50	0.08	12.5	1.1
20/200	6/60	4/40	0.10	10.0	1.0
20/160	6/48	4/32	0.125	8.0	0.9
20/125	6/38	4/25	0.16	6.3	0.8
20/100	6/30	4/20	0.20	5.0	0.7
20/80	6/24	4/16	0.25	4.0	0.6
20/63	6/20	4/12.6	0.32	3.2	0.5
20/50	6/15	4/10	0.40	2.5	0.4
20/40	6/12	4/8	0.50	2.0	0.3
20/32	6/10	4/6.4	0.63	1.6	0.2
20/25	6/7.5	4/5	0.80	1.25	0.1
20/20	6/6	4/4	1.0	1.0	0
20/16	6/5	4/3.2	1.25	0.8	− 0.1
20/12.5	6/3.75	4/2.5	1.60	0.63	− 0.2
20/10	6/3	4/2	2.0	0.5	− 0.3

Snellen Visual Acuity in meters and feet, decimal notation, MAR, and logMAR.
ETDRS charts are based on linear LogMAR score.
[a] MAR, minimal angle of resolution (minute of arc).

[redacted]

8.2.6. Summary of Efficacy Endpoint Analyses

Endpoint	Analysis Set	Assessment	PLANNED Statistical Method	Missing Data	Interpretation
Change in maximum cystometric bladder capacity at week 12 relative to baseline	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics and subgroup summaries.	BOCF/LOCF (for ANCOVA only)	Primary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics and subgroup summaries.	BOCF/LOCF (for ANCOVA only)	Primary analysis (for Cohort 2)
	PPAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	No imputation	Supportive to the primary analysis (for Cohort 1)
	PPAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	No imputation	Supportive to the primary analysis (for Cohort 2)
Change in maximum detrusor pressure at maximum bladder capacity at week 12 relative to baseline	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 2)
Presence of IDC	FAS (Cohort 1)	Week 12	Categorical summaries	BOCF/LOCF	Secondary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	Categorical summaries	BOCF/LOCF	Secondary analysis (for Cohort 2)
	PPAS (Cohort 1)	Week 12	Categorical summaries	No imputation	Secondary analysis (for Cohort 1)

Endpoint	Analysis Set	Assessment	PLANNED Statistical Method	Missing Data	Interpretation
	PPAS (Cohort 2)	Week 12	Categorical summaries	No imputation	Secondary analysis (for Cohort 2)
Change in bladder compliance at week 12 relative to baseline	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 2)
	PPAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	No imputation	Secondary analysis (for Cohort 1)
	PPAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	No imputation	Secondary analysis (for Cohort 2)
Change in Bladder volume at first IDC at week 12 relative to baseline	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 2)
Change in mean number of micturitions per 24 hours at Week 12 relative to baseline.	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 2)
Change in mean number of incontinence episodes per 24	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 1)

Endpoint	Analysis Set	Assessment	PLANNED Statistical Method	Missing Data	Interpretation
hours at Week 12 relative to the baseline	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 2)
Change in mean number of urgency episodes per 24 hours at Week 12 relative to the baseline	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 2)
Change in mean voided volume per micturition at Week 12 relative to baseline.	FAS (Cohort 1)	Week 12	ANCOVA – hypothesis testing approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 1)
	FAS (Cohort 2)	Week 12	ANCOVA – estimation approach; Descriptive statistics.	BOCF/LOCF (for ANCOVA only)	Secondary analysis (for Cohort 2)

9. REFERENCES

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

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

[redacted]

10. APPENDIX

10.1. APPENDIX A: SCHEDULE OF EVENTS

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

[redacted]

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

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

[redacted]

10.2. Appendix B: DEFINITION OF ASSESSMENT WINDOWS

There will be no visit windows defined for this study. The target observation will be that taken at a time closest to when the scheduled visit should have occurred.

The LOCF1 rule will be used to impute data at missing visits (ie, the last non-missing reading prior to the window will be used; the observation does not have to have fallen inside a window).

Diary data should be completed within +/- 14 days of a visit whether this is a formal visit or a withdrawal visit.

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