Protocol A0221109

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

Statistical Analysis Plan (SAP)

Version: 2.1

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Summary of changes is described in Table 1. No changes spoiling the integrity of this clinical study are included.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 05 Jun 2015	Original 28 Jan 2015	N/A	N/A
2.0 6 April 2020	None	Minor changes to clarify the detailed analysis plan	• The objective of "to investigate the efficacy of fesoterodine following once daily long-term treatment in Japanese pediatric NDO subjects" was set as secondary objective in accordance with the protocol version 1. • Description of treatment misallocations were minor changed to clarify the treatment group used in the analyses. • Efficacy endpoints of "Mean number of micturitions/24hours", "Mean number of catheterizations/24hours" and "Mean number of micturitions and catheterizations combined/24hours" were changed to analyze for the subjects with >0 episodes at baseline of Study A0221047, in accordance with A0221047 SAP version 2.0. • Remove an endpoint of "Presence of subtraction test (eg, cough) on urodynamic trace" in accordance with A0221047 SAP version 2.0. • The definition of treatment emergent was changed for AE occur in oxybutinine-treatment period and become more severe; evaluation period of AE was changed from the period in A0221109 to the fesoterodine treatment period from A0221047 in Section 6.2.1. • To clarify that Demographics and baseline characteristics data would be summarized based on baseline information of the A0221047. • To clarify that observed values and change from baseline in efficacy

			endpoints would be provided in listings. • To clarify the analysis of onset time of AEs. • Analysis of GPT was changed in accordance with A0221047 SAP version 2.0. • Change visit window definition appropriately.
2.1 9 April 2020	None	Minor error was revised	• The date of SAP was changed from 6 Apr 2019 to 9 Apr 2020.

2. INTRODUCTION

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

This document describes the statistical analysis plan for the safety and efficacy.

Drug Development Rationale

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

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

Children with NDO therefore represent a disease population with a need for an alternative effective, safe and well-tolerated therapy to help manage the overactive detrusor, reducing or preventing incontinence, as well as the high pressure bladder contractions that can result in UUT (upper urinary tract) *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 objective of this study is to investigate the safety and tolerability of fesoterodine PR (prolonged release) *tablet 4 mg and 8 mg once daily for 1 year in pediatric NDO subjects*

aged between 6-17 years with a body weight >25 kg, and fesoterodine BIC (beads-in-capsule) *2 mg and 4 mg in subjects ≤25 kg.*

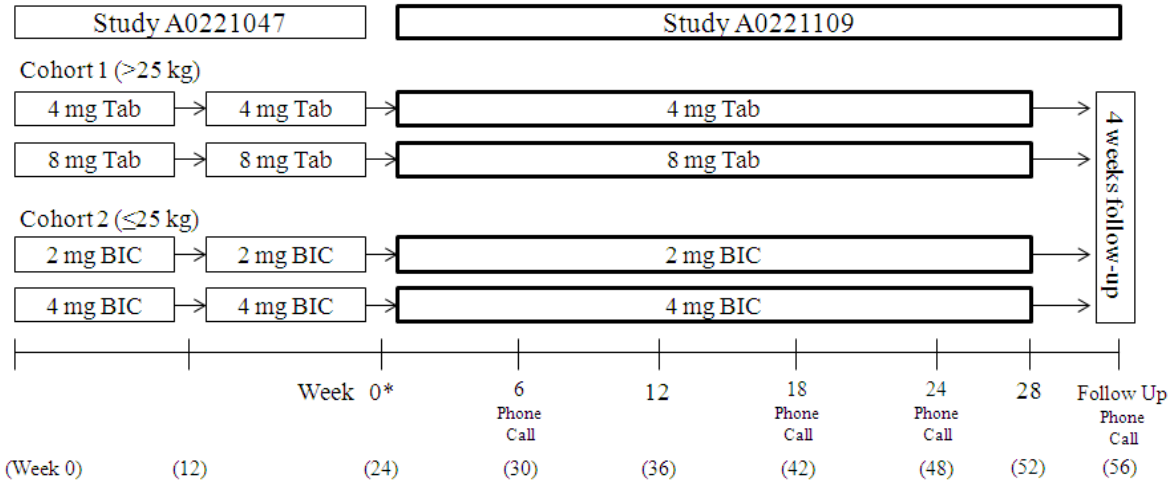
2.1. Study Design

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

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

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

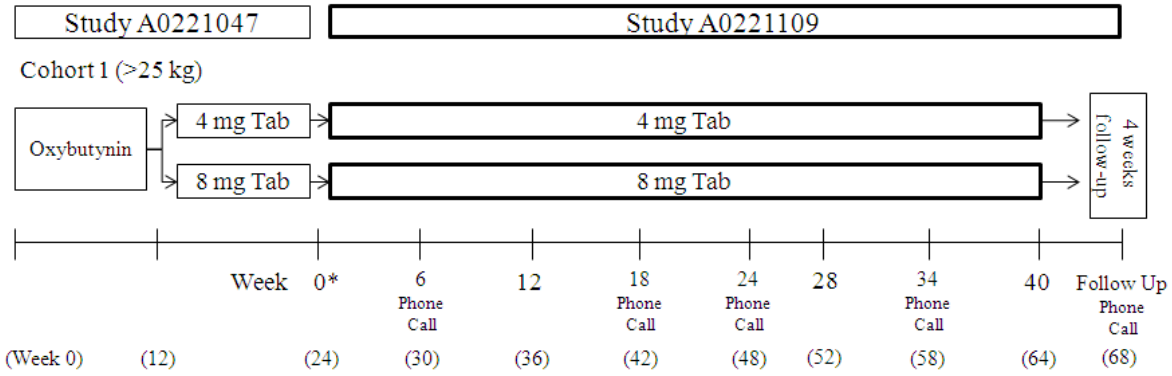
Figure 1. Study Design (Subjects who were randomized to Fesoterodine arms in Study A0221047)



( ) weeks from baseline of Study A0221047

** Week 0 visit is the same visit as Week 24 visit of Study A0221047.*

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



( ) weeks from baseline of Study A0221047

** Week 0 visit is the same visit as Week 24 visit of Study A0221047.*

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

Subjects >25 kg who cannot swallow tablets are not permitted to take the BIC formulation and are excluded from the study. Even if the body weight of subjects with ≤25 kg at baseline of the precedent Study A0221047 increase >25 kg during Study A0221047 or this study, they should maintain the same dose and formulation.

2.2. Study Objectives

Primary Objective

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

Secondary Objective

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

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis will be planned in this study.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There are no statistical hypotheses.

4.2. Statistical Decision Rules

There are no statistical decision rules.

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set will include all subjects who have been enrolled and received at least one dose of study medication and have at least 1 observation in efficacy endpoint data after baseline visit in Study A0221109.

The Full Analysis Set (FAS) will be used for all efficacy analyses.

For all efficacy analyses, the data from Study A0221047 and Study A0221109 will be merged (see the details in Section 8.1).

5.2. 'Per Protocol' Analysis Set

Not applicable.

5.3. Safety Analysis Set

The Safety Analysis Set will include all subjects who have been enrolled and received at least one dose of study medication in Study A0221109.

For analyses of adverse events, the data from Study A0221047 and Study A0221109 will be merged (see the details in Section 8.1).

5.4. Other Analysis Sets

None.

5.5. Treatment Misallocations

Subjects who are enrolled but never treated in Study A0221109 will not be included in either safety or efficacy analyses. For an enrolled subject who took the incorrect treatment (i.e., a subject who does not start dosing with the randomized dose in Study A0221047), he/she will be reported under the randomized treatment group in Study A0221047 for all efficacy analyses, but will be reported under the treatment they actually received for all safety analyses.

If misallocations already occurred in Study A0221047, the definition determined in Study A0221047 is followed. Hence, 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

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure and a decision taken regarding evaluation for each analysis population.

At enrollment, the investigator will assess patients against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

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

- *Detrusor pressure at maximum bladder capacity.*

- *Presence of IDC* (involuntary detrusor contractions)

- *Bladder volume at first IDC, if present.*

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

- *Mean number of micturitions/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 of Study A0221047.

- *Mean number of catheterizations/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 of Study A0221047.

- *Mean number of micturitions and catheterizations combined/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. This endpoint will only be calculated for subjects with >0 episodes at baseline of Study A0221047.

*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 incontinence episodes/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 incontinence episodes at baseline of Study A0221047.

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

  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 urgency episodes at baseline of Study A0221047.

- *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 or 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

6.2. Safety Endpoints

- *Adverse events, including monitoring of targeted events including, but not limited to:*
    - *Serious adverse event.*
    - *Anticholinergic effects such as dry mouth, dry eyes and constipation.*
    - *Central nervous system (CNS) effects such as behavioral changes (eg, aggression), decreased cognitive function, headache, seizures, somnolence.*
    - *Visual effects such as accommodation disorder, blurred vision, and amblyopia.*
- *Visual acuity and accommodation tests.*
- *Cognitive function by the Child Behavior Checklist (CBCL) and Grooved Pegboard Test (GPT).*
- *Vital Signs, including heart rate in the context of age-appropriate norms.*
- *Urinary Tract Infection (UTI), as evidenced by urinalysis, urine microscopy, culture and sensitivity.*
- *Clinical Laboratory Evaluations in the context of age-appropriate norms, with particular reference to liver function tests and renal chemistry.*
- *Post-void residual volume (PVR) in subjects not performing clean intermittent catheterization (CIC), or with >1 UTI during the study.*

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.

Any events occurring following the start of study drug of fesoterodine or increasing in severity will be counted as treatment emergent. Events that occur in the oxybutynin-treatment period in Cohort 1 of Study A0221047 will NOT be attributed to fesoterodine, unless they started in the oxybutynin-treatment period in Cohort 1 of Study A0221047 and became more severe in the fesoterodine-treatment period.

6.2.2. Vital Signs

Blood pressure, temperature and pulse rate should be measured at each clinic visit. This schedule of measurements should provide adequate indication of any clinically relevant changes. However, if vital signs show a clinically relevant change from baseline of Study A0221047, then safety monitoring will occur at a minimum of monthly intervals, or more

frequently as clinically appropriate, until the abnormality resolves. The measured results will be assessed in the context of age appropriate norms.

Temperature may be taken via oral, tympanic or axillary routes as per local accepted practice. Digital devices are permitted; however, mercury thermometers should not be used. The same method as Study A0221047 should be used for the subject throughout the study.

Blood pressure should be measured using a pediatric or appropriately sized sphygmomanometer in the sitting/resting position with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg. The same arm (preferably the dominant arm) as Study A0221047 will be used throughout the study.

The same size blood pressure cuff as Study A0221047, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

6.2.3. Physical Examination

A physical examination will be performed at each clinic visit, and will include the following systems:

- *General appearance (including weight);*
- *Skin;*
- *Head, eyes, ears, nose, and throat; including visual acuity and accommodation (see Section 6.2.5);*
- *Respiratory;*
- *Cardiovascular;*
- *Gastrointestinal;*
- *Musculoskeletal;*
- *Neurological.*

If physical examinations show a clinically relevant change from baseline of the precedent Study A0221047, then safety monitoring will occur at a minimum of monthly intervals, or more frequently as clinically appropriate, until the abnormality resolves. Any clinically significant negative changes from the entry examination will be recorded as adverse events.

6.2.4. Weight Measurements

Weight will be recorded at each clinic visit. All weight measurements should be standardized using the same equipment and measuring technique for an individual subject. Any clinically significant change in weight should be reported as an adverse event.

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

6.2.5. Visual Acuity and Accommodation

Visual acuity will be assessed for each eye using the Snellen method, using an optotype that is appropriate to the child's intellectual development at each clinic visit.

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

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

6.2.6. Post-Void Residual Volume (PVR)

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

Assessment of PVR in subjects performing CIC should also be carried out in the event that they experience >1 UTI during the Study A0221047 and this study.

6.2.7. Clinical Laboratory Evaluation

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

Table 2. ***Safety Laboratory***

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

a. When indicated, the investigator may request calculation of an estimated GFR using the Schwartz equation GFR = (k x H)/Cr where k = constant, H = Height (length) and Cr = Creatinine. In this case, the laboratory will need to be provided with the subject's height in cm.

b. Urine microscopy, culture and sensitivity to be performed in the event of the presence of symptoms (eg, fever, flank pain), positive leucocytes and/or nitrites on urinalysis, or if the subject has a documented history of vesicoureteral reflux (VUR).

c. Females of childbearing potential only (≥9 years old or have experienced menarche, whichever is earlier). Pregnancy tests may also be repeated as per request of Institutional Review Board (IRB)/Ethics Committee (EC) or if required by local regulations.

6.2.8. Childhood Behavior Checklist (CBCL)

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

The CBCL will be completed at each clinic visit.

6.2.9. Grooved Pegboard Test (GPT)

The GPT is a manipulative dexterity test that assesses psychomotor speed, fine motor control, and rapid-visual motor coordination. It consists of a small board of 25 holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the

hole before they can be inserted. Time to completion, number of pegs dropped, and number of pegs placed correctly are scored.

The GPT will be assessed at each clinic visit.

6.3. Other Endpoints

None.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

No imputation for missing data will be planned in efficacy and safety analysis.

In the case that the data of patient's background in Study A0221047 is used for the analysis of this study, handling of missing data in Study A0221047 will be employed in this study.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Efficacy endpoints and treatment-emergent adverse events will be summarized using merged data of Study A0221047 and Study A0221109. When the longitudinal changes are analyzed for the merged data, baseline will be Visit 1 (Screening) or Visit 2 (Day 1) of Study A0221047. Demographics and baseline characteristics including medical history, prior drug/Non-drug treatments will use baseline information at Visit 1 (Screening) or Visit 2 (Day 1) of Study A0221047. Other safety endpoints will be summarized for the data of Study A0221109 alone, and baseline will be Week 0 of Study A0221109.

Treatments will be labeled as follows:

Cohorts of Study A0221047 (for analysis using the merged data of Study A0221047 and A0221109)

Cohort 1

Cohort 2

Treatment groups of Study A0221047 (for analysis using the merged data of Study A0221047 and A0221109, demographics and baseline characteristics)

Fesoterodine 4 mg Tab

Fesoterodine 8 mg Tab

Oxybutynin->Fesoterodine 4 mg Tab

Oxybutynin->Fesoterodine 8 mg Tab

Fesoterodine 2 mg BIC

Fesoterodine 4 mg BIC

Treatment group at baseline in Study A0221109 (for analysis using the data of Study A0221109 alone)

Fesoterodine 4 mg Tab (A0221109)

Fesoterodine 8 mg Tab (A0221109)

Fesoterodine 2 mg BIC (A0221109)

Fesoterodine 4 mg BIC (A0221109)

The cohorts and the treatment groups of Study A0221047 will be used for data summaries of efficacy endpoints and treatment-emergent adverse events. The treatment groups at baseline in Study A0221109 will be used for data summaries of the safety endpoints excluding adverse events, although the dosage can be reduced to the lower dose at each clinic visit for subjects on the higher dose.

8.1.1. Analyses for Continuous Data

Continuous data will be summarized using descriptive statistics. The following will be presented: number of subjects, arithmetic mean, standard deviation, median, minimum, and maximum.

8.1.2. Analyses for Categorical and Binary Data

Categorical and binary data will be presented using cell counts and percentages for each category. For summaries of change from baseline, the tables will be presented as a cross tabulation with baseline visit along the side and results of each visit along the top.

8.2. Statistical Analyses

8.2.1. Analysis of Efficacy Data

For the following efficacy analyses, data will be summarized for the total of treatment groups, each cohort and each treatment group of Study A0221047, using the merged data of Study A0221047 and Study A0221109. *Subgroup analyses will be conducted that exclude oxybutynin treatment group in cohort 1 of A0221047 from* the total *for all efficacy endpoints if any subjects who were randomized to oxybutynin group in A0221047 are in FAS.*

All efficacy endpoints of continuous data and their change from baseline will be summarized descriptively by each visit according to 8.1.1.

The presence of IDC will be summarized by each visit according to 8.1.2.

Listing tables will be provided at each timepoint from baseline visit of A0221047 to final visit of this study for all efficacy endpoints of observed values and changes from baseline *with*

subjects information (ie., subject ID, gender, age, body weight at baseline of A0221047, cohort of A0221047, randomized treatment group in A0221047 and treatment history from the A0221047 start to the end of this study).

8.2.2. Analysis of Safety Data

Tables and listings of safety and demographic data, including adverse events and medical history will be reported in accordance with current Pfizer standards using baseline information at start of A0221047.

Treatment emergent adverse events will be summarized for the total of treatment groups, each cohort and each treatment group of Study A0221047, using the merged data of Study A0221047 and Study A0221109. Treatment emergent adverse events (PT; preferred term) will be also summarized by the period of the onset time from the start of the fesoterodine treatment (0 – 12 weeks (1-84 days), 13 – 24 weeks (85-168 days), 25 – 36 weeks (169-252 days), in or after 37 weeks (>= 253 days)).

For the following safety analyses, data will be summarized for each treatment group at baseline of Study A0221109, using the data of Study A0221109 alone.

Vital Signs

Blood pressure and pulse rate and their change from baseline will be summarized descriptively for each treatment group, by each visit according to 8.1.1.

Listings of all vital signs will also be created.

Visual Acuity and Accommodation

Visual acuity (LogMAR units) and accommodation (the distance for each eye at which vision becomes blurred – the mean of triplicate measurements) and their change from baseline will be summarized descriptively for each label, by each visit according to 8.1.1.

Listings of visual acuity and accommodation will also be created.

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.

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).

PVR

PVR and their change from baseline will be summarized descriptively for each label, by each visit according to 8.1.1.

Listings of PVR will also be created.

Clinical Laboratory Evaluation

The incidence of laboratory abnormalities observed at any time during the study will be tabulated following PDS and summary statistics for changes from baseline will be provided by each visit.

Listings of clinical laboratory evaluation will also be created.

CBCL

CBCL(Domain T Scores and Total Scores as captured in the CRF) and their change from baseline will be summarized descriptively for each label, by each visit according to 8.1.1.

Listings of CBCL will also be created.

GPT

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) and their change from baseline will be summarized descriptively for each label, by each visit according to 8.1.1.

Listings of GPT will also be created.

8.2.3. Summary of Efficacy Endpoint Analyses

Table 3. Summary of Efficacy Endpoint Analyses

Endpoint	**Analysis Set**	**Assessment**	**Planned Statistical Method**	Missing Data	Objective
Change in maximum cystometric capacity at each visit relative to baseline	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment
Change in detrusor pressure at maximum bladder capacity at each visit relative to baseline	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment
Presence of IDC	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Categorical summaries	No imputation	Efficacy following long-term treatment
Change in bladder volume at first IDC at each visit	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment
Change in bladder compliance at each visit relative to baseline	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment

Table 3. Summary of Efficacy Endpoint Analyses

Endpoint	**Analysis Set**	**Assessment**	**Planned Statistical Method**	Missing Data	Objective
Change in mean number of micturitions and catheterizations/24 hours at each visit relative to baseline	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment
Change in mean number of incontinence episodes/24 hours at each visit relative to the baseline	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment
Change in mean number of urgency episodes/24 hours at each visit relative to the baseline	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment
Change in mean voided volume per micturition or catheterization at each visit relative to baseline	FAS	Week 12 Week 52 (for Fesoterodine arm in Study A0221047) Week 64 (for Oxybutynin arm in Study A0221047) Final Visit	Continuous summaries	No imputation	Efficacy following long-term treatment

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.

10. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Definition and Use of Visit Windows in Reporting

There were no visit windows defined for Study A0221047. The target observation of "Week 12 from Day 1 of Study A0221047" will also be that taken at a time closest to when the scheduled visit should have occurred.

Visit windows for after Study A0221109 are defined.

Table 4. Visit Windows for Efficacy Endpoints

Visit Label	Endpoint	Definition [Day window]
A0221047:Day1	Urodynamic Assessments Bladder Diary	Same definitions of A0221047 will be used.
A0221047:Week12	Urodynamic Assessments Bladder Diary	Same definitions of A0221047 will be used.
A0221047:Week52/ A0221109:Week28	(for Fesoterodine arms in Study A0221047) Urodynamic Assessments Bladder Diary	= An assessment where 'Date of assessment' – 'Date Day 1 of Study A0221047' + 1 = [310, 407]
A0221047:Week 64/ A0221109:Week40	(for Oxybutynin arm in Study A0221047) Urodynamic Assessments Bladder Diary	= An assessment where 'Date of assessment' – 'Date Day 1 of Study A0221047' + 1 = [408, 491]
Final Visit	Urodynamic Assessments Bladder Diary	= The last assessment where 'Date of assessment' – 'Date Day 1 of Study A0221047' + 1 > 169

Table 5. Visit Windows for Safety Endpoints

Visit Label	Endpoint	Definition [Day window]
A0221047:Week24/ A0221109:Day1	Vital Signs Visual Acuity and Accommodation PVR Clinical Laboratory Evaluation CBCL GPT	= An assessment where 'Date of assessment' – 'Date Week 0 of Study A0221109' + 1 is in [-20, 42]
A0221047:Week36/ A0221109:Week12	Vital Signs Visual Acuity and Accommodation PVR Clinical Laboratory Evaluation CBCL GPT	= An assessment where 'Date of assessment' – 'Date Week 0 of Study A0221109' + 1 is in [43, 140]
A0221047:Week52/ A0221109:Week28	Vital Signs Visual Acuity and Accommodation PVR Clinical Laboratory Evaluation CBCL GPT	= An assessment where 'Date of assessment' – 'Date Week 0 of Study A0221109' + 1 is in [141, 238]
A0221047:Week64/ A0221109:Week40	(for Oxybutynin arm in Study A0221047) Vital Signs Visual Acuity and Accommodation PVR Clinical Laboratory Evaluation CBCL GPT	= An assessment where 'Date of assessment' – 'Date Week 0 of Study A0221109' + 1 is in [239, 322]
Final Visit	Vital Signs Visual Acuity and Accommodation PVR Clinical Laboratory Evaluation CBCL GPT	= The last assessment after 'Date of assessment' – 'Date Week 0 of Study A0221109' + 1 >= 43