Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 022030 / S-019
Link to EDR	\\CDSESUB1\evsprod\NDA022030\0151 [SDN 1460 (12/18/2020); SDN 1474 (3/22/2020), SDN 1477 (4/2/2021), SDN 1481 (4/21/2021), and SDN 1488 (5/19/2021)]
Submission Date	12/18/2020
Submission Type	Prior Approval Effiacay Supplement / Priority Review
Brand Name	Toviaz® Extended Release (ER) Tablets
Generic Name	Fesoterodine fumarate
Dosage Form and Strength	Toviaz® ER tablets: 4 mg and 8 mg
Route of Administration	Oral
Proposed Indication	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 6 years of age and older with a body weight ≥ (b) (4) kg.
Applicant	Pfizer
Associated IND	IND 051232
OCP Review Team	Chongwoo Yu, PhD Junshan Qiu, PhD Jingyu (Jerry) Yu, PhD Yanhui Lu, PhD
OCP Final Signatory	Yanhui Lu, PhD Team Leader Division of Cardiometabolic and Endocrine Pharmacology (DCEP), Office of Clinical Pharmacology (OCP)
OND Division	Division of Urology, Obstetrics and Gynecology (DUOG)

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1. EXECUTIVE SUMMARY

The Applicant submitted a post approval efficacy supplement new drug application (sNDA) for Toviaz® (fesoterodine fumarate) extended release (ER) tablets on December 18, 2020 to seek approval for a new indication of the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 6 years of age and older with a body weight ≥ (b) (4) kg.

Fesoterodine (Toviaz®) is a muscarinic antagonist that has been approved for the treatment of overactive bladder (OAB) in adults with symptoms of urge urinary incontinence, urgency, and frequency on October 31, 2008. The currently approved recommended starting dose of fesoterodine is 4 mg once daily (QD). Based on individual response and tolerability, the dose may be increased to 8 mg QD. The daily dose of Toviaz in adults should not exceed 4 mg in the following populations:

- Patients with severe renal impairment (creatinine clearance [CL_{CR}] < 30 mL/min])
- Patients taking potent cytochrome P450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin.

Toviaz® is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). Toviaz® should be taken with liquid and swallowed whole. Toviaz® can be administered with or without food.

The proposed dosage regiment for the new NDO indication is as follows:

- 4 mg QD in pediatric patients 6 years of age and older weighing (b) (4) -35 kg.
- 8 mg QD in pediatric patients 6 years of age and older weighing >35 kg.

In the following pediatric patients 6 years of age and older, the Applicant is proposing not to recommend Toviaz® for use in patients weighing (b) (4) -35 kg, and is recommending to reduce Toviaz® dose to 4 mg QD in pediatric patients weighing > 35 kg:

- Patients with severe renal impairment (CL_{CR} <30 mL/min)
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin

The Applicant conducted 3 relative bioavailability (BA)/pharmacokinetics (PK) studies, 1 Phase 2, dose-escalating study, and 1 Phase 3 study and its long-term extension study to support the approval of the proposed NDO indication in pediatrics. In addition, 4 population PK / exposure-response (E-R) analysis reports were submitted. (b) (4)

1.1 Recommendations

The Office of Clinical Pharmacology (OCP)/Division of Cardiometabolic and Endocrine Pharmacology (DCEP) and the Division of Pharmacometrics (DPM) reviewed NDA 022030 / S-019 submitted on December 18, 2020, March 22, 2021, April 2, 2021, April 21, 2020, and May 19, 2021. The overall Clinical Pharmacology information submitted to support this sNDA is **acceptable** and Toviaz® is **recommended for approval with the revision of Dosage and Administration recommendations** for the indication of NDO in pediatric patients 6 years of age and older **weighing greater than 25 kg** from the Clinical Pharmacology standpoint.

Key Clinical Pharmacology review issues with specific recommendations/comments are summarized in Table 1 below:

Table 1: Key Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	• The efficacy and safety of Toivaz ER tablets were deminstrated in pediatric patients (6-17 years old) with NDO in the Phase 3 study (A0221047) and and its long-term extension study (A0221109). • The Phase 2, dose-escalation study (A0221066), population PK analyses, and the E-R analyses provided supportive evidence.
General dosing instructions	The recommended dosage for pediatric patients aged 6 years and older with NDO is as follows: • ***Pediatric patients weighing greater than 25 kg and up to 35 kg***: The recommended dosage of Toviaz® is 4 mg orally QD. If needed, dosage may be increased to Toviaz® 8 mg orally QD. • ***Pediatric patients weighing greater than 35 kg***: The recommended starting dosage of Toviaz® is 4 mg orally QD. After 1 week, increase to Toviaz® 8 mg orally QD.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• ***Pediatric patients weighing greater than 25 kg and up to 35 kg***: Toviaz® is not recommended in patients with severe renal impairment or those taking strong CYP3A4 inhibitors. • ***Pediatric patients weighing greater than 35 kg***: Toviaz® is recommended to be reduced to 4 mg QD in patients with severe renal impairment or in those taking strong CYP3A4 inhibitors.
Labeling	Refer to Section 2.4 for the review team's recommendations.
Bridge between the to-be-marketed and clinical study formulations	The Phase 3 study (A0221047) was conducted using the currently approved commercial formulation.
Other (specify)	None

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Fesoterodine is a competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), which is responsible for the antimuscarinic activity of fesoterodine.

Muscarinic receptors play a role in contractions of urinary bladder smooth muscle. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects.

Absorption:
After oral administration in healthy adults, fesoterodine is well absorbed. Due to rapid and extensive hydrolysis by nonspecific esterases to its active metabolite 5-HMT, fesoterodine cannot be detected in plasma. BA of the active metabolite is 52%. After single or multiple-dose oral administration of fesoterodine in doses from 4 mg to 28 mg, plasma concentrations of the active metabolite are proportional to the dose. Maximum plasma concentrations are reached after approximately 5 hours. No accumulation occurs after multiple-dose administration. There is no clinically relevant effect of food on the PK of fesoterodine. The PK of fesoterodine were not significantly influenced by age, gender, or race.

For a pediatric patient (from 6 years to 17 years of age) with NDO weighing 35 kg with a CYP2D6 extensive metabolizer (EM) status receiving Toviaz® tablets, the mean values of apparent oral clearance, volume of distribution and absorption rate constant of 5-HMT are estimated to be approximately 72 L/h, 68 L and 0.09 h-1, respectively. The T_{max} and half-life of 5-HMT are estimated to be approximately 2.55 h and 7.73 h, respectively. Like adults, the 5-HMT exposure in CYP2D6 poor metabolizers (PMs) was estimated to be approximately 2-fold higher compared with EMs. The post-hoc estimaes of steady-state exposures of 5-HMT in NDO patients weighing greater than 25 kg following Toviaz® 4 mg and 8 mg tablets QD are summarized in Table 2.

Table 2: Summary of Geometric Mean [%CV] PK Parameters for the Active Metabolite After Steady-State Dosing of Fesoterodine in Pediatric Patients with NDO, Ages 6-17 years Weighing Greater Than 25 kg

Dosage	N	$C_{max,ss}$ (ng/mL)	$AUC_{tau,ss}$ (ng*h/mL)
4 mg once daily	32	4.88 (48.2)	59.1 (51.7)
8 mg once daily	39	8.47 (41.6)	103 (46.2)

CV = coefficient of variation; $C_{max,ss}$ = steady-state maximum plasma concentration,
$AUC_{tau,ss}$ = steady-state area under the concentration time curve over the 24-hour dosing interval,
N = number of patients with PK data

Distribution
Plasma protein binding of the active metabolite is low (approximately 50%) and is primarily bound to albumin and alpha-1-acid glycoprotein. The mean steady-state volume of distribution following intravenous infusion of the active metabolite is 169 L.

Metabolism
After oral administration, fesoterodine is rapidly and extensively hydrolyzed to its active metabolite, 5-HMT. 5-HMT is further metabolized in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites via two major pathways involving CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine. A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are PMs for CYP2D6. C_{max} and AUC of the active metabolite are increased 1.7- and 2-fold, respectively, in CYP2D6 PMs, as compared to EMs.

Excretion
Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite, 5-HMT. After oral administration of fesoterodine, approximately 70% of the administered dose was recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) was recovered in feces. The terminal half-life of the active metabolite is approximately 4 hours following an intravenous administration. The apparent terminal half-life following oral administration is approximately 7 hours.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Toviaz® should be swallowed as whole with liquid. Do not chew, divide, or crush. Take with or without food

The recommended dosage for pediatric patients aged 6 years and older with NDO is as follows:

Pediatric patients weighing greater than 25 kg and up to 35 kg: The recommended dosage of Toviaz® is 4 mg orally QD. If needed, dosage may be increased to Toviaz® 8 mg orally QD.

Pediatric patients weighing greater than 35 kg: The recommended starting dosage of Toviaz® is 4 mg orally QD. After one week, increase to Toviaz® 8 mg orally QD.

The recommended dosage in pediatric patients with renal impairment is as follows:

Pediatric patients weighing greater than 25 kg and up to 35 kg: The recommended dosage of Toviaz® in pediatric patients with renal impairment weighing greater than 25 kg and up to 35 kg is described in Table 3.

Table 3: Toviaz® Recommended Dose in Pediatric Patients Aged 6 Years and Older Weighing Greater than 25 kg and up to 35 kg with Renal Impairment (Administered Orally QD)

Estimated Glomerular Filtration Rate (eGFR)[1]	**Recommended Dose**
eGFR 30 to 89 mL/min/1.73 m^2	4 mg
eGFR 15 to 29 mL/min/1.73 m^2	Use is Not Recommended
eGFR <15 mL/min/1.73 m^2 or requiring dialysis	Use is Not Recommended

[1] Estimate GFR using a validated GFR estimating equation for the pediatric age range of the approved indication.
[2] Dosing was derived assuming similar proportional effects of renal impairment in adults and pediatric patients 6 years and older.

Pediatric patients weighing greater than 35 kg: The recommended dosage of Toviaz® in pediatric patients with renal impairment weighing greater than 35 kg is described in Table 4.

Table 4: Toviaz® Recommended Dose in Pediatric Patients Aged 6 Years and Older Weighing Greater Than 35 kg with Renal Impairment (Administered Orally QD)

Estimated GFR[1]	**Recommended Dose**
eGFR 30 to 89 mL/min/1.73 m^2	8 mg[2]
eGFR 15 to 29 mL/min/1.73 m^2	4 mg
eGFR <15 mL/min/1.73 m^2 or requiring dialysis	Use is Not Recommended

[1] Estimate GFR using a validated GFR estimating equation for the pediatric age range of the approved indication.
[2] The recommended starting dosage of Toviaz is 4 mg orally QD. After one week, increase to the recommended dosage of Toviaz® 8 mg orally QD.
[3] Dosing was derived assuming similar proportional effects of renal impairment in adults and pediatric patients 6 years and older.

The following Toviaz® dosage modifications are recommended due to strong CYP3A4 inhibitors:

Pediatric patients with NDO weighing greater than 25 kg and up to 35 kg: The use of Toviaz® in pediatric patients weighing greater than 25 kg and up to 35 kg and taking strong CYP3A4 inhibitors is not recommended.

Pediatric patients with NDO weighing greater than 35 kg: The maximum recommended dosage is Toviaz® 4 mg orally QD in pediatric patients weighing greater than 35 kg and taking strong CYP3A4 inhibitors.

2.2.2 Therapeutic individualization

Renal Impairment
In adult patients with severe renal impairment (CL_{CR} <30 mL/min), C_{max} and AUC of 5-HMT are increased 2.0- and 2.3-fold, respectively. Doses of Toviaz® greater than 4 mg are not recommended in patients with severe renal impairment. In adult patients with mild or moderate renal impairment (CL_{CR} ranging from 30-80 mL/min), C_{max} and AUC of the 5-HMT are increased up to 1.5- and 1.8-fold, respectively, as compared to healthy adult subjects. No dose adjustment is recommended in adult patients with mild or moderate renal impairment.

In pediatric patients, the increase in median C_{max} and AUC of 5-HMT with mild renal impairment (CL_{CR} 60-89 mL/min or eGFR 60-89 mL/min/1.73 m^2; 4 subjects in Cohort 1 of Study A0221047 and 3 subjects in Study A0221066) were within 2-fold, compared with those with normal renal function (CL_{CR} > 90 mL/min or eGFR > 90 mL/min/1.73 m^2). Subjects with clinically significant renal disease were not eligible to participate in the Phase 2 study, A0221066 and subjects with clinically relevant out-of-range serum creatinine values were excluded from the Phase 3 study, A0221047.

In general, for children over the age of 2 years, kidney function maturation is considered complete. Since the target pediatric population for this supplement are 6 years of age and older and no dose adjustment is needed in adult patients with mild or moderate renal impairment, assuming similar proportional effects of renal impairment in adults and the pediatric patients, no dose adjustment is recommended in pediatric patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2). Because 2-fold or higher C_{max} and AUC was observed in adults with severe renal impairment compared to adults with normal renal function and the recommended dose of Toviaz® in these adult patients is reduced to 4 mg (from 8 mg which is recommended for patients with normal renal function), Toviaz® dose in pediatric patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) weighing > 35 kg is recommended to be reduced from 8 mg to 4 mg, and Toviaz® is not recommended for use in pediatric patients with kidney failure (eGFR < 15 mL/mL/1.73 m^2 or requiring dianlysis) and in pediatric patients with severe renal impairment weigheing 25 to 35 kg.

Hepatic Impairment
Adult patients with severe hepatic impairment (Child-Pugh C) have not been studied; therefore Toviaz® is not recommended for use in these patients. Since pediatric patients with severe hepatic impairment were excluded from the Phase 3 study, A0221047, Toviaz® is not recommended for use in pediatric patients with severe hepatic impairment.

In adult patients with moderate (Child-Pugh B) hepatic impairment, C_{max} and AUC of 5-HMT are increased 1.4- and 2.1-fold, respectively, as compared to healthy adult subjects. No dose adjustment is recommended in adult patients with mild or moderate hepatic impairment. Since the metabolic capacity of liver in pediatric patients 6 years of age and older is expected to be similar to that in adults, no dose adjustment is recommended in pediatric patients with mild or moderate hepatic impairment.

Drug Interactions
The C_{max} and AUC of 5-HMT from a single dose of Toviaz® 8 mg increased 2.0- and 2.3-fold, respectively, after oral administration of a strong CYP3A4 inhibitor, ketoconazole, 200 mg twice daily (BID) for 5 days in adult CYP2D6 EMs. Likewise, in adult CYP2D6 PMs, C_{max} and AUC of 5-HMT increased 2.1- and 2.5-fold, respectively, during coadministration of ketoconazole 200 mg BID for 5 days. Doses of Toviaz® greater than 4 mg are not recommended in adult patients taking strong CYP3A4 inhibitors. Pediatric patients required to take or expected to initiate concomitant administration with strong CYP3A4 inhibitors were excluded from the Phase 3 study, A0221047. As mentioned above, the metabolic capacity of liver in pediatric patients 6 years of age and older is expected to be similar to that in adults. To ensure that 5-HMT exposure would be maintained within a well-tolerated range in pediatric patients taking strong CYP3A4 inhibitors, it is recommended to reduce the dose by half to account for the approximately 2-fold increase in 5-HMT exposure. Thus, for pediatric patients weighing > 35 kg, fesoterodine dose is recommended to be reduced to 4 mg QD in patients taking strong CYP3A4 inhibitors. For pediatric patients with body weight greater than 25 kg and up to 35 kg, fesoterodine administration is not recommended in patients taking strong CYP3A4 inhibitors. No dose adjustments are recommended in the presence of CYP3A4 inducers or CYP2D6 inhibitors.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Clinical Pharmacology review team's labeling recommendations include the following:

Section 2 Dosage & Administration

- Revised the entire section together with DUOG and the Division of Pediatrics and Maternal Health (DPMH) for clarity of dosage recommendations in different subgroups and to be consistent with the format of dosage recommendations for pedfiatric patients with other drug products.
- For renal impairment catgorization, used creatinine clearance for adults to be consistent with how renal impairment studies were done; while for pediatric patients, used estimated GFR in units normalized by body surface area which is more appropriatefor the pediatric patients compared to the Applicant's proposal of using creatinine clearance without accounting for body surface area.

Section 12.3 Pharmacokinetics

- Added information regarding PK in pediatric patients.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Product

Toviaz® contains fesoterodine fumarate and is an ER tablet (same as the approved product for the OAB indication in adults). Fesoterodine is rapidly de-esterified to its active metabolite, 5-HMT, which is a muscarinic receptor antagonist. Muscarinic receptors play a role in contractions of urinary bladder smooth muscle and stimulation of salivary secretion. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects.

Regulatory History

Toviaz® was approved for the treatment of OAB in adults with symptoms of urge urinary incontinence, urgency, and frequency on October 31, 2008. At the time of approval, Toviaz® was approved with a post marketing requirement under the Pediatric Research Equity Act (PREA), as follows:

- Deferred pediatric study under PREA for the treatment of overactive bladder in the subgroup of pediatric patients with neurologic disease ages 6 to 16 years, 11 months.

A Written Request (WR) was issued on November 14, 2011, followed by WR amendments on May 19, 2014, October 3, 2016, and June 27, 2019, in efforts to resolve enrollment and recruitment, and manufacturing process challenges. Reference is made to the minutes of the September 10, 2020 pre-sNDA meeting. (b) (4)

The purpose of this supplement is to seek approval for a new indication for the treatment of NDO in pediatric patients 6 years of age and older with body weight ≥ (b) (4) kg for the ER tablet formulation that is currently approved for the adult OAB indication.

Clinical Deveopment Porgram

To support the approval of Toviaz® in the pediatric population with NDO, there were 3 relative BA/PK studies, 1 Phase 2, dose-escalation study, and 1 Phase 3 study and its long-term extension study conducted. An overview of the completed clinical studies included in the submission is provided in Tables 5 and 6. Additionally, 4 population PK / E-R analysis reports were submitted as outlined in Table 7.

Table 5: Summary of Fesoterodine Pediatric NDO Clinical Development Program

Type of Study	Study Title and Description	Status (number of participants enrolled)
Phase 1 PK/ RBA Studies	A0221068: An open-label, single-dose, randomized, crossover study to estimate the bioavailability and food effect of 4 mg fesoterodine ER BIC formulations compared to commercial tablet in healthy adult volunteers	Completed (N = 20)
	A0221069: An open-label, single-dose, randomized, crossover study to estimate the effects of food on the PK of 2 fesoterodine SR BIC formulations and to estimate the relative bioavailability of one or both formulations compared to commercial tablet in healthy adult volunteers.	Completed (N = 24)
	A0221099: An open-label, single-dose, randomized, crossover study to estimate the relative bioavailability of 5-HMT following single oral doses of fesoterodine SR BIC formulations compared to commercial fesoterodine extended-release tablet formulation and the effects of food or sprinkling on applesauce for fesoterodine SR BIC formulations in healthy adult volunteers.	Completed (N = 24)
Phase 2 PK/ Safety Study	A0221066: An open-label, dose-escalating study of the PK, safety, and tolerability of fesoterodine in pediatric overactive bladder patients aged 8 to 17 years.	Completed (N = 21)[a]
Phase 3 Efficacy and Safety Study	A0221047: A 24-week randomized, open-label study to evaluate the safety and efficacy of fesoterodine in participant aged 6 to 17 years with symptoms of detrusor overactivity associated with a neurological condition (Neurogenic Detrusor Overactivity)	Completed (Cohort 1, N = 124; Cohort 2, N = 57)
Phase 3 Long-Term Safety Study	A0221109: A long-term extension study to evaluate the safety of fesoterodine in Japanese pediatric participants with symptoms of detrusor overactivity associated with a neurological condition (Neurogenic Detrusor Overactivity) who have completed 24 weeks treatment in Study A0221047	Completed (Cohort 1, N = 2; Cohort 2, N = 10)

Source: Study Reports A0221068, A0221069, A0221099, A0221066, A0221047, and A0221109
Abbreviations: N = number of participants; RBA = relative bioavailability; SR = sustained release
Cohort 1: >25 kg; Cohort 2: ≤25 kg
[a] OAB N=10; NDO N=11

Source: Table 1, Module 2.7.2

Table 6: Overview of Phase 2 and 3 Pediatric Studies

Study No/ Status Phase Country/Region (No. of Sites)	Study Title and Description	Study Medication	Number of Randomized Subjects by Treatment Group
Randomized, Open-Label Clinical Study			
1047/ Completed Phase 3 Global (65)	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)	Cohort 1 (>25 kg): fesoterodine 4 or 8 mg tablets QD or oxybutynin XL (≥10 mg QD)	Cohort 1: Feso 4 mg tablet: 42; Feso 8 mg tablet: 42; Oxy: 40
		Cohort 2 (≤25 kg): fesoterodine 2 or 4 mg BIC	Cohort 2: Feso 2 mg BIC; Feso 4 mg BIC (b) (4)
Open-Label Extension Study			
1109/ Completed Phase 3 Japan (7)	A 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 1047	Cohort 1(>25 kg): fesoterodine 4 or 8 mg tablets QD	Cohort 1: Feso 4 mg tablet: 0; Feso 8 mg tablet: 2
		Cohort 2 (≤25 kg): fesoterodine 2 or 4 mg BIC	Cohort 2: Feso 2 mg BIC; Feso 4 mg BIC (b) (4)
PK Study			
1066/ Completed Phase 2 US (7)	An open-label, dose-escalating study of the PK, safety and tolerability of fesoterodine in pediatric OAB and NDO patients aged 8 to 17 years	fesoterodine 4 or 8 mg QD (subjects were administered both doses)	Feso 4 mg tablet: 21; Feso 8 mg tablet: 20

Source: Table 1, Module 2.5

Table 7: Overview of PK Modeling & Simulation Reports

Title	Description	Study Number(s)
PMAR-00216 (Appended to the CSR for Study A0221066)	Preliminary Population PK analysis of 5-HMT in pediatric participants age 8-17 yrs	A0221066
PMAR-EQDD-A022a-Other-296	Clinical trial simulations to determine fesoterodine dosing in Phase 3 Study A0221047 for pediatric participants age 6-17 yrs weighing ≤25 kg and >25 kg	A0221066, A0221047[a]
PMAR-EQDD-A022a-Other-1068	Population PK analysis of 5-HMT in pediatric participants age 6-17 yrs	A0221066, A0221047
PMAR-EQDD-A022a-Other-1069	Exposure-response analysis of maximum cystometric capacity in fesoterodine-treated pediatric participants with NDO, age 6-17 yrs	A0221047

Source: PMAR-00216, PMAR-EQDD-A022a-Other-296, PMAR-EQDD-A022a-Other-1068, and PMAR-EQDD-A022a-Other-1069

[a]Available data from Cohort 1 participants were used for comparison of observed PK results and those predicted by clinical trial simulations

Source: Table 2, Module 2.7.2

3.2 General Pharmacology and Pharmacokinetic Characteristics

Table 8: General Pharmacology and PK Chacteristics

Pharmacology	
Mechanism of Action	Fesoterodine is a competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine, which is responsible for the antimuscarinic activity of fesoterodine. Muscarinic receptors play a role in contractions of urinary bladder smooth muscle. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects.
Active Moieties	Fesoterodine and 5-HMT (active metabolite)
QT Prolongation	Fesoterodine at doses of 4 and 28 mg/day did not prolong the QT interval.
General Information	
Bioanalysis	A liquid chromatography – tandem mass spectrometry (LC-MS/MS) method was used to measure plasma 5-HMT concentrations.
Healthy vs. Patients	No comparison of PK between pediatric NDO patients and healthy pediatrics was conducted.
PK	
PK in Pediatrics	
Estimated 5-HMT PK Parameters[a]	Mean values of apparent oral clearance, volume of distribution and absorption rate constant of 5-HMT are estimated to be approximately 72 L/h, 68 L and 0.09 h^{-1}, respectively. The T_{max} and half-life of 5-HMT are estimated to be approximately 2.6 h and 7.7 h, respectively.
Post-hoc Estimates of 5-HMT exposure at steady state (Geometric mean [%CV])[b]	$AUC_{tau,ss}$ for 4 mg QD: 59.1 (47.6) ng·h/mL (N=32) $C_{max,ss}$ for 4 mg QD: 4.88 (44.0) ng/mL (N=32) $AUC_{tau,ss}$ for 8 mg QD: 103.0 (45.0) ng·h/mL (N=39) $C_{max,ss}$ for 8 mg QD 8 47 (39 4) ng/mL (N 39)
Metabolism	
Human Metabolism Pathways	After oral administration, fesoterodine is rapidly and extensively hydrolyzed to its active metabolite, 5-HMT. 5-HTM is further metabolized in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites via two major pathways involving CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine.

Variability in CYP2D6 Metabolism	A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are PMs for CYP2D6. C_{max} and AUC of 5-HMT are increased 1.7- and 2-fold, respectively, in CYP2D6 PMs, as compared to extensive metabolizers.
Excretion	
Primary excretion pathways (% dose)	Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite. After oral administration of fesoterodine, approximately 70% of the administered dose was recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) was recovered in feces.
Terminal half-life	The terminal half-life of 5-HMT is approximately 4 hours following an intravenous administration. The apparent terminal half-life following oral administration is approximately 7 hours.

[a] For a pediatric patient (from 6 years to 17 years of age) with NDO weighing 35 kg with a CYP2D6 EM status receiving Toviaz® tablets.
[b] In pediatric patients with NDO, ages 6-17 years weighing greater than 25 kg

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The Phase 2 study, A0221066, was an 8-week, open-label, uncontrolled, dose-escalation study that evaluated the PK and safetystudy of fesoterodine 4 mg and 8 mg QD in 20 pediatric participants with OAB (age 8 to 17 years and weighing > 25 kg). Approximately 50% of the study population was comprised of participants with NDO. Starting dose was 4 mg QD (Week 1-4) and was escalated to 8 mg QD (Weeks 5-8). The key Clinical Pharmacology information obtained from this study was as follows:

- Variability in 5-HMT PK was primarily affected by body weight, and clearance of 5-HMT was similar in pediatric participants compared to adults when allometrically scaled by patient weight (64.5 L/hr vs 60.6 L/hr, respectively).
- The observed concentrations of 5-HMT in the pediatric patients were comparable to those in adults at the approved doses.

The Phase 3 study, A0221047 was a randomized, open-label study to evaluate the efficacy, safety, PK, and tolerability of fesoterodine in participants aged 6 to 17 years with symptoms of NDO. The study consisted of 2 parts as follows:

- Part 1: 12 week 3-arm phase with active comparator (oxybutynin XL release)
- Part 2: 12 week, 2-arm phase without active comparator

The treatment cohorts were:

- Cohort 1 (> 25 kg): 4 mg and 8 mg ER tablets or oxybutynin XL release (3 arms)
- Cohort 2 (25 kg or less): 2 mg and 4 mg sustained release (SR) BIC (2 arms)

The key study outcomes were as follows:

- Like adults, the 5-HMT exposures in CYP2D6 PMs were estimated to be approximately 2-fold higher compared with extensive metabolizers.
- The primary efficacy analyses of change from baseline to Week 12 in maximum cystometric bladder capacity (MCBC) demonstrated that treatment with Toviaz® 8 mg or Toviaz® 4 mg resulted in improvements in MCBC with numerically higher changes from baseline for Toviaz® 8 mg than for Toviaz® 4 mg. Results of urodynamic or patient urinary diaries-derived secondary efficacy endpoints were generally supportive of the improvements from baseline observed.

Based on the results of efficacy and safety from the Phase 3 study, A0221047, as well as modeling and simulation analyses, the Applicant proposed fesoterodine 4 and 8 mg ER tablets as the recommended pediatric formulation with a dosing regimen of fesoterodine 4 mg QD for patients with a body weight ≥ [(b) (4)] kg to ≤ 35 kg and of fesoterodine [(b) (4)] mg QD for patients with a body weight >35 kg. The Applicant's rationale for this dosing recommendation is based on maintaining 5-HMT exposures (maximum observed concentration at steady state [$C_{max,ss}$] and area under the concentration time curve at steady state [$AUC_{tau,ss}$]) in pediatric patients receiving fesoterodine 4 and 8 mg ER tablet QD doses within an efficacious and well-tolerated range of exposure closer to adult values.

However, due to the reasons described in Section 3.3.2, the Clinical Pharmacology review team recommends the dosage regimen as outlined in Section 2.2.1 of ths review.

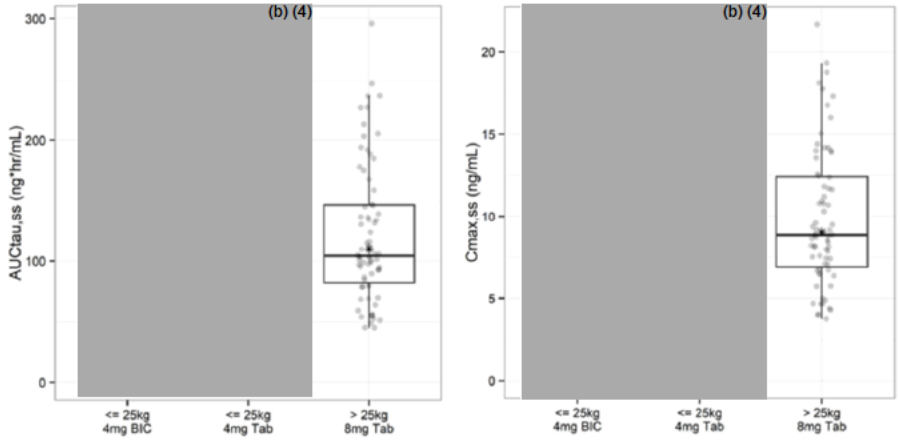
3.3.2 Is the proposed dosage regimen appropriate for the general patient population for which the indication is being sought?

No. The proposed 4 mg QD dose for patients weighing [(b) (4)] kg is not appropriate due to insufficient supporting information. While the Applicant proposed only the 4 mg QD dose for patients weighing > 25 kg to 35 kg, the review team recommends that the dose of 4 mg QD may be increased to 8 mg QD if needed. In addition, the proposed [(b) (4)] mg QD dose for pediatric patients weighing >35 kg should be revised to have a starting dosage at 4 mg QD and increase to 8 mg QD after one week.

The Applicant took the approach of maintaining $C_{max,ss}$ values within a well-tolerated range with $C_{max,ss}$ and $AUC_{tau,ss}$ values closer to adults as an index of safety for both 4 mg and 8 mg ER tablet QD doses.

As noted in Figure 1, simulated $C_{max,ss}$ [(b) (4)] patients > 25 kg receiving Toviaz® 8 mg tablets QD. However, 5-HMT $C_{max,ss}$ estimates in some pediatric patients weighing > 25 kg up to 35 kg, following Toviaz® 8 mg tablets QD, exceeded the maximum value of adult $C_{max,ss}$ (17.7 ng/mL) as estimated by the adult final population PK model (Figure 2). In addition, the median $C_{max,ss}$ value in this group following Toviaz® 8 mg QD is estimated to be 11.7 ng/mL, which is 2.45 times of that in adults receiving 8 mg QD (4.78 ng/mL). The Applicant believes that [(b) (4)] the body weight threshold [(b) (4)] 35 kg in pediatric participants would result [(b) (4)] in 5-HMT exposure, to the point at which it would be comparable to the range of exposure ($C_{max,ss}$ and $AUC_{tau,ss}$) estimatd in adults receiving the 8 mg tablet (Figure 3).

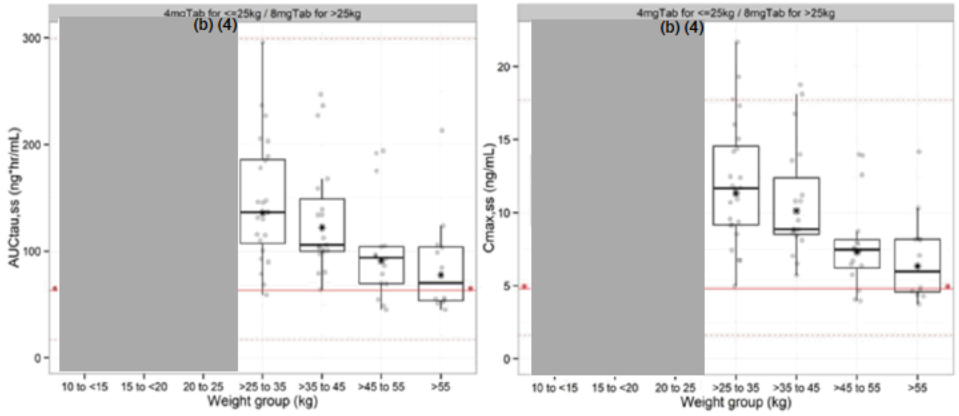
Figure 1: Comparison of Simulated Estimates of $AUC_{tau,ss}$ and $C_{max,ss}$ in NDO Pediatric Participants in Study A0221047



Repository step ID CP1:ST-9636342. For each box, median value for each metric ($AUC_{tau,ss}$ or $C_{max,ss}$) is designated by a black line in the center of the box. Boxes indicate the IQR. Whiskers represent 1.5·IQR. Jitter dots are actual values to visualize the distribution of each metric in each group. The stars represent geometric mean values for each metric.

Source: Figure 3, Module 2.7.2

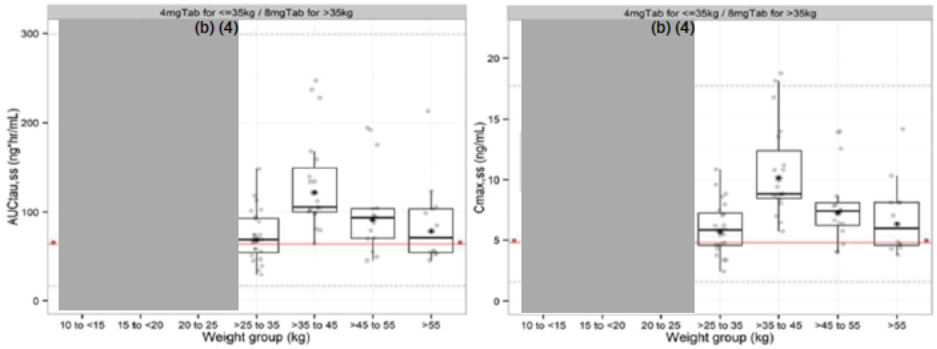
Figure 2: Distribution of Simulated Estimates of $AUC_{tau,ss}$ and Following Administration of Fesoterodine 4 mg/8 mg Tablet QD in Study A0221047, Based on 25 kg Body Weight Threshold



Repository step ID CP1:ST-10291411. For each box, median value for each metric ($AUC_{tau,ss}$ or $C_{max,ss}$) is designated by a black line in the center of the box. Boxes indicate the IQR. Whiskers represent 1.5 IQR. Jitter dots are actual values to visualize the distribution of each metric in each group. The stars in each box represent geometric mean value for each metric. Red solid lines (dotted lines) represent median (range) values for each metric estimated for adults in fesoterodine program, whereas red stars at right and left ends of each figure represent corresponding geometric mean values.

Source: Figure 4, Module 2.7.2

Figure 3: Distribution of Simulated Estimates of $AUC_{tau,ss}$ and $C_{max,ss}$ Following Administration of Fesoterodine 4/8 mg Tablet QD in Study A0221047, Based on 35 kg Body Weight Threshold



Repository step ID CP1:ST-10291468. For each box, median value for each metric ($AUC_{tau,ss}$ or $C_{max,ss}$) is designated by a black line in the center of the box. Boxes indicate the IQR. Whiskers represent 1.5 IQR. Jitter dots are actual values to visualize the distribution of each metric in each group. The stars in each box represent geometric mean value for each metric. Red solid lines (dotted lines) represent median (range) values for each metric estimated for adults in fesoterodine program, whereas red stars at right and left ends of each figure represent corresponding geometric mean values.

Source: Figure 5, Module 2.7.2

The Applicant believes (b) (4)

The Pharmacometrics review team has verified the Applicant's analyses without finding any significant discordance and concludes that the Applicant's analyses support their proposal of changing the weight threshold from (b) (4) kg to 35 kg. However, due to the following reasons, the Clinical Pharmacology review team (including the Pharmacometrics review team) does not concur with the Applicant's proposed Dosage & Administrations recommendations and have the recommendations as follows:

- (b) (4)
  .
- ***Pediatric patients weighing greater than 25 kg up to 35 kg***: For this group, both 4 mg and 8 mg QD treatments have been evaluated in the Phase 3 study, A0221066. Treatments with both 4 mg or 8 mg QD resulted in improvements from baseline to Week 12 in the primary efficacy endpoint, maximum cystometric bladder capacity (MCBC), with numerically higher changes from baseline for the 8 mg QD treatment than for the 4 mg QD treatment. However, since some patients in this group receiving Toviaz 8 mg QD may have higher $C_{max,ss}$ compared to adults (see Figure 2 above), the Clinical Pharmacology review team recommends the dosage of 4 mg QD for this group and if needed, dosage may be increased to 8 mg QD.
- ***Pediatric patients weighing greater than 35 kg***: The Clinical Pharmacology review team recommends the starting dosage of 4 mg QD. After one week, dosage should be increased to 8 mg QD as the Phase 3 study was conducted.

3.3.3 Is there a management strategy required for subpopulations based on intrinsic factors?

Yes.

Renal Impairment

In adult patients with severe renal impairment (CL_{CR} <30 mL/min), C_{max} and AUC of 5-HMT are increased 2.0- and 2.3-fold, respectively. Doses of Toviaz® greater than 4 mg are not recommended in patients with severe renal impairment. In adult patients with mild or moderate renal impairment (CL_{CR} ranging from 30-80 mL/min), C_{max} and AUC of 5-HMT are increased up to 1.5- and 1.8-fold, respectively, as compared to healthy adult subjects. No dose adjustment is recommended in patients with mild or moderate renal impairment.

Currently accepted and validated equations in common clinical use for estimating renal function in pediatric patients are estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2 (b) (4) (b) (4) Upon the Clinical Pharmacology review team's request, the Applicant submitted their revised proposal for the Dosage & Administration recommendations for pediatric patients with renal impairment using eGFR (in units of mL/min/1.73 m^2) with their justification on May 19, 2021 (SDN: 1488).

Subjects with clinically significant renal disease were not eligible to participate in the Phase 2 study, A0221066, and subjects with clinically relevant out-of-range serum creatinine values were excluded in the Phase 3 study, A0221047. As with the Toviaz® adult program, the creatinine clearance in pediatric patients in Studies A0221066 and A0221047 was calculated using the Cockroft-Gault (C-G) formula. Of note, in the Phase 3 study, A0221047, height was not assessed per protocol. For some subjects in Study A0221047, at the request of the Investigator, eGFR was calculated using the bedside Schwartz formula (eGFR = [k x H]/CR, where k = constant with a value of 0.413, H = height [length] and CR = serum creatinine concentration), a commonly used equation for estimation of renal function in pediatric patients (Muhari-Stark and Burckart, *J Pediatr Pharmacol Ther*. 2018). In the Phase 2 study, A0221066, height was assessed for all subjects therefore eGFR has been calculated using the bedside Schwartz formula for these subjects. The Applicant believes that the C-G formula has been shown to be the best prediction of GFR, as measured by inulin clearance, when compared with the bedside Schwartz and Modification of Diet in Renal Disease (MDRD) formulas in adolescents 12 years of age and older. Using the bedside Schwartz formula alone, limited data were available for evaluation in Study A0221047. Therefore, renal impairment determination was based on eGFR calculated using the bedside Schwartz formula for subjects less than 12 years old (where available), and the C-G formula for subjects aged 12 years of age and older which is what is recommended in the FDA *Draft Guidance on General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (2014). Renal impairment severity categorization was undetermined for subjects less than 12 years old who did not have an available eGFR based on the bedside Schwartz formula.

Tables 9 and 10 lists of subjects who were determined to have renal impairment from Study A0221066, Study A0221047 - Cohort 1.

Table 9: Participants with Renal Impairment in Study A0221066

Subject ID	Age	Sex	CL_{CR} (mL/min)	Renal Class based on CL_{CR}	eGFR (bedside Schwartz) (mL/min/1.73 m^2)	Renal Class based on eGFR (bedside Schwartz)	eGFR (MDRD) (mL/min/1.73 m^2)	Renal Class based on eGFR (MDRD)
(b) (6)	17	F	86.5	Mild	68.8	Mild	73.9	Mild
	9	F	71.2	Mild	76.4	Mild	119.5	Normal
	9	M	92.9	Normal	82.9	Mild	177.8	Normal

Source: Table 16.2.8.1.2, SDN 1488 (May 19, 2021)

Table 10: Participants with Renal Impairments in Study A0221047

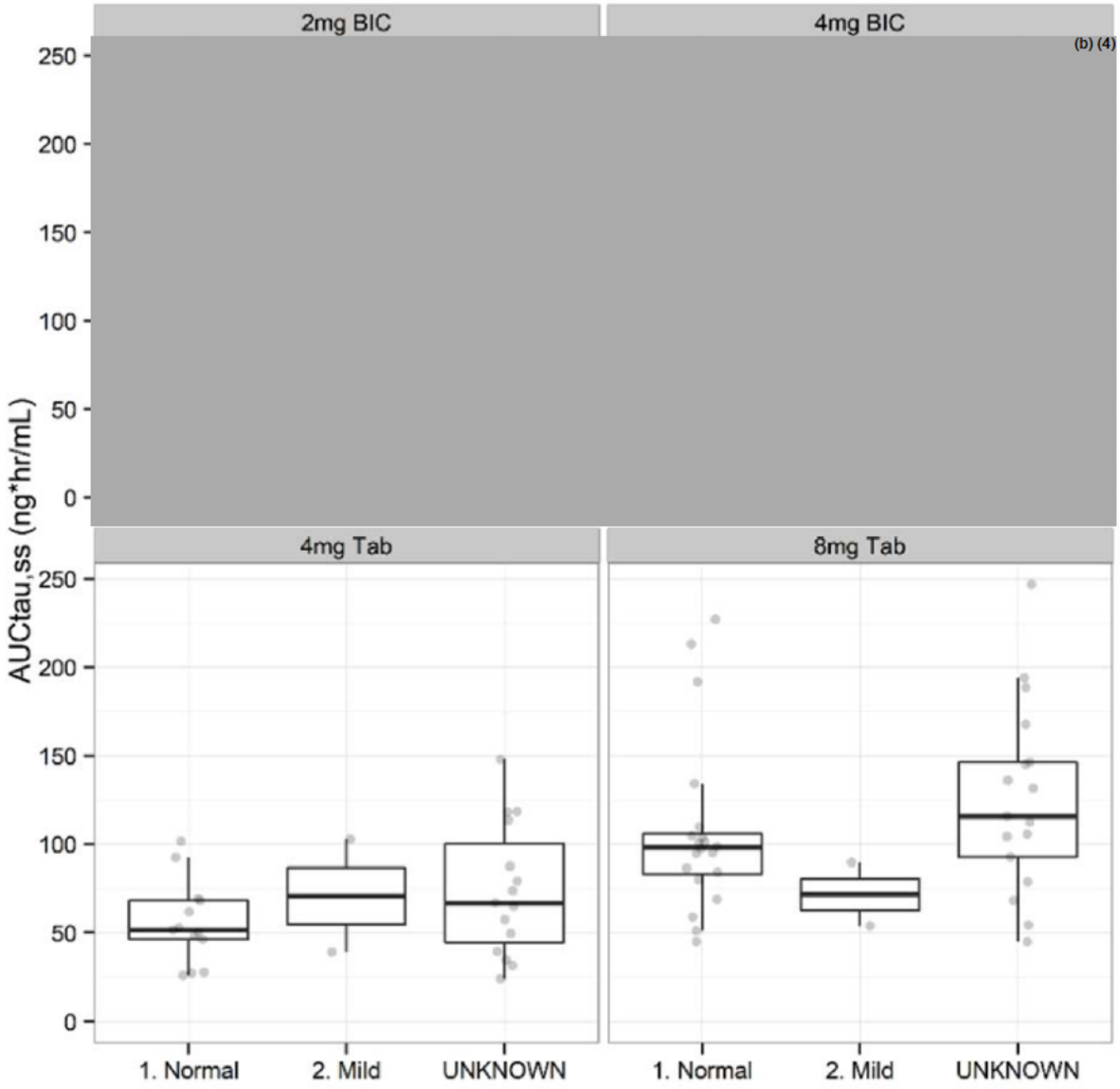
Subject ID	Age	Sex	Fesoterodine Dose Group	CL_{CR} (mL/min)	Renal Class based on CL_{CR}	eGFR (bedside Schwartz) (mL/min/1.73 m^2)	Renal Class based on eGFR (bedside Schwartz)	eGFR (MDRD) (mL/min/1.73 m^2)	Renal Class based on eGFR (MDRD)
(b) (6)	7	M	4 mg	86.2	Mild	86	Mild	212.6	Normal
	9	F	4 mg	120.4	Normal	81	Mild	125.5	Normal
	16	F	8 mg	89.1	Mild	N/A	N/A	59.9	Moderate
	15	M	8 mg	86.1	Mild	83	Mild	152.4	Normal

Source: Table 16.2.8.1.2a,, SDN 1488 (May 19, 2021)

For most of the subjects, the renal class determined based on eGFR from the bedside Schwartz equation appears to be the most conservative among the 3 different methods compared in Tables 9 and 10. The increase in C_{max} and AUC of 5-HMT in pediatric patients with mild renal impairment (CL_{CR} 60-89 mL/min or eGFR 60-89 mL/min/1.73 m^2) (4 subjects in Cohort 1 of Study A0221047 and 3 subjects in Study A0221066) appears not to be clinically significant, with a similar range of exposures and median C_{max} and AUC values within 2-fold, compared with those in patients with normal renal function (CL_{CR} > 90 mL/min or eGFR > 90 mL/min/1.73 m^2). In addition, in the Phase 3 study, A0221047, patients with mild renal impairment receiving fesoterodine did not experience adverse events with any change in frequency or severity compared to those patients with normal or undetermined renal function as far as can be determined within the limitations of the sample sizes. Therefore, no dose adjustment is recommended for pediatric patients with mild renal impairment.

In general, for children over the age of 2 years, kidney function maturation is considered complete. Since the target pediatric population for this supplement are 6 years of age and older and as no dose adjustment is needed in adult patients with moderate renal impairment, assuming similar proportional effects of renal impairment in adults and the pediatric patients, no dose adjustment is recommended in pediatric patients with moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2). Because 2-fold or higher C_{max} and AUC was observed in severe renal impairment in adults compared to adults with normal renal function and the recommended dose of Toviaz® in these adult patients is reduced to 4 mg (from 8 mg which is recommended for patients with normal renal function), Toviaz® dose in pediatric patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) weighing > 35 kg is recommended to be reduced from 8 mg to 4 mg, and Toviaz® is not recommended for use in pediatric patients with kidney failure (eGFR < 15 mL/mL/1.73 m^2 or requiring dianlysis) and in pediatric patients with severe renal impairment weigheing 25 to 35 kg.

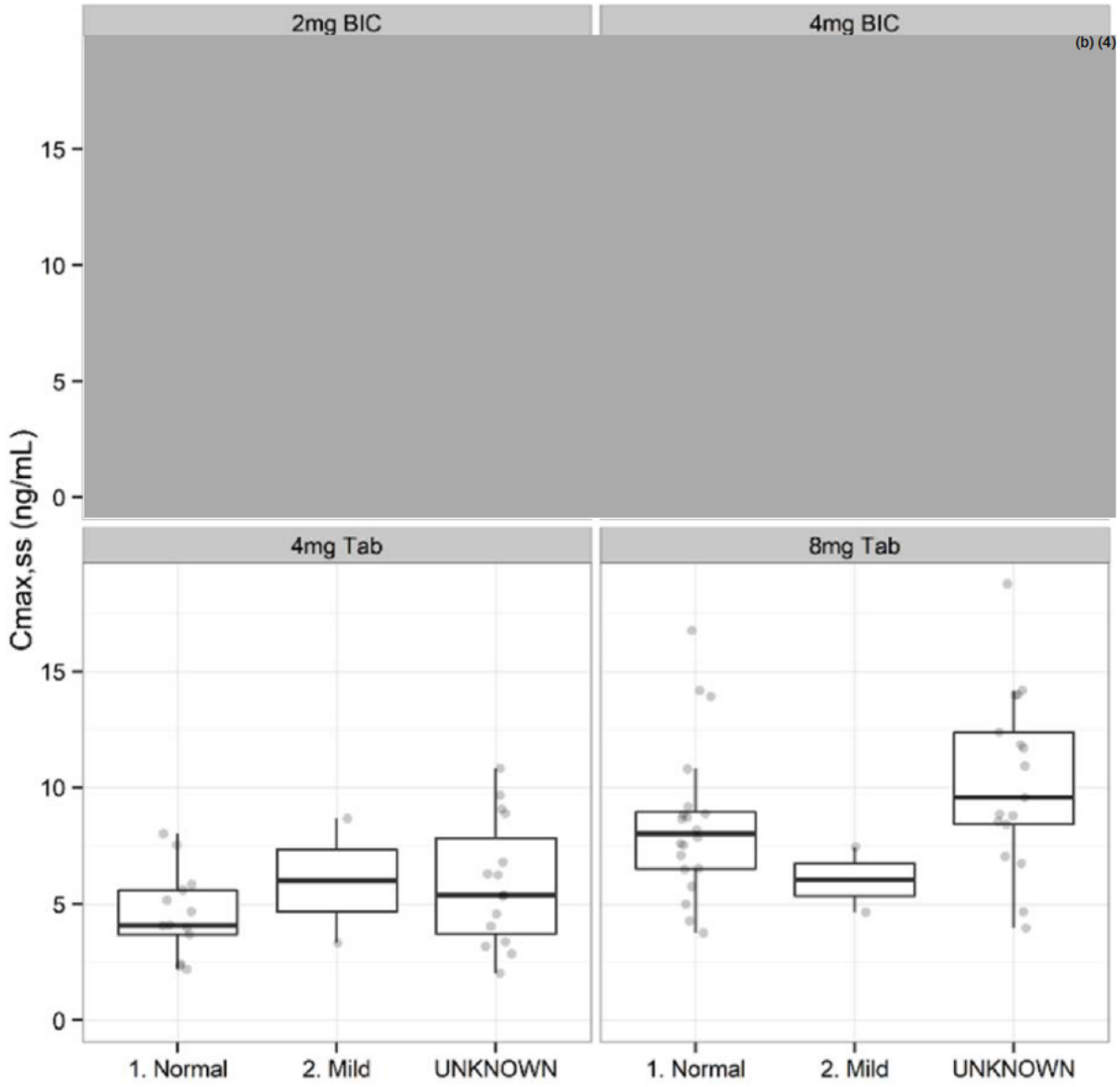
Figure 4: Effect of Renal Impairment on the Estimated 5-HMT Exposures (AUCtau,ss) in Study A0221047



Repository step ID CP1:ST-19156059. BIC: Beads in Capsule. Tab: Tablet. Renal function classified based on Clcr calculated using Cockroft-Gault equation for subjects ≥12 years, and eGFR calculated using Schwartz equation for subjects 6-11 years. $AUC_{tau,ss}$ values were estimated based on empirical Bayes estimates following dosing of fesoterodine 4 or 8 mg tablet QD or 2 or 4 mg BIC QD. For each box, median value for $AUC_{tau,ss}$ is designated by a black line in the center of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Jitter dots are actual values to visualize the distribution of each metric in each group.

Source: Figure 1, SDN 1488 (May 19, 2021)

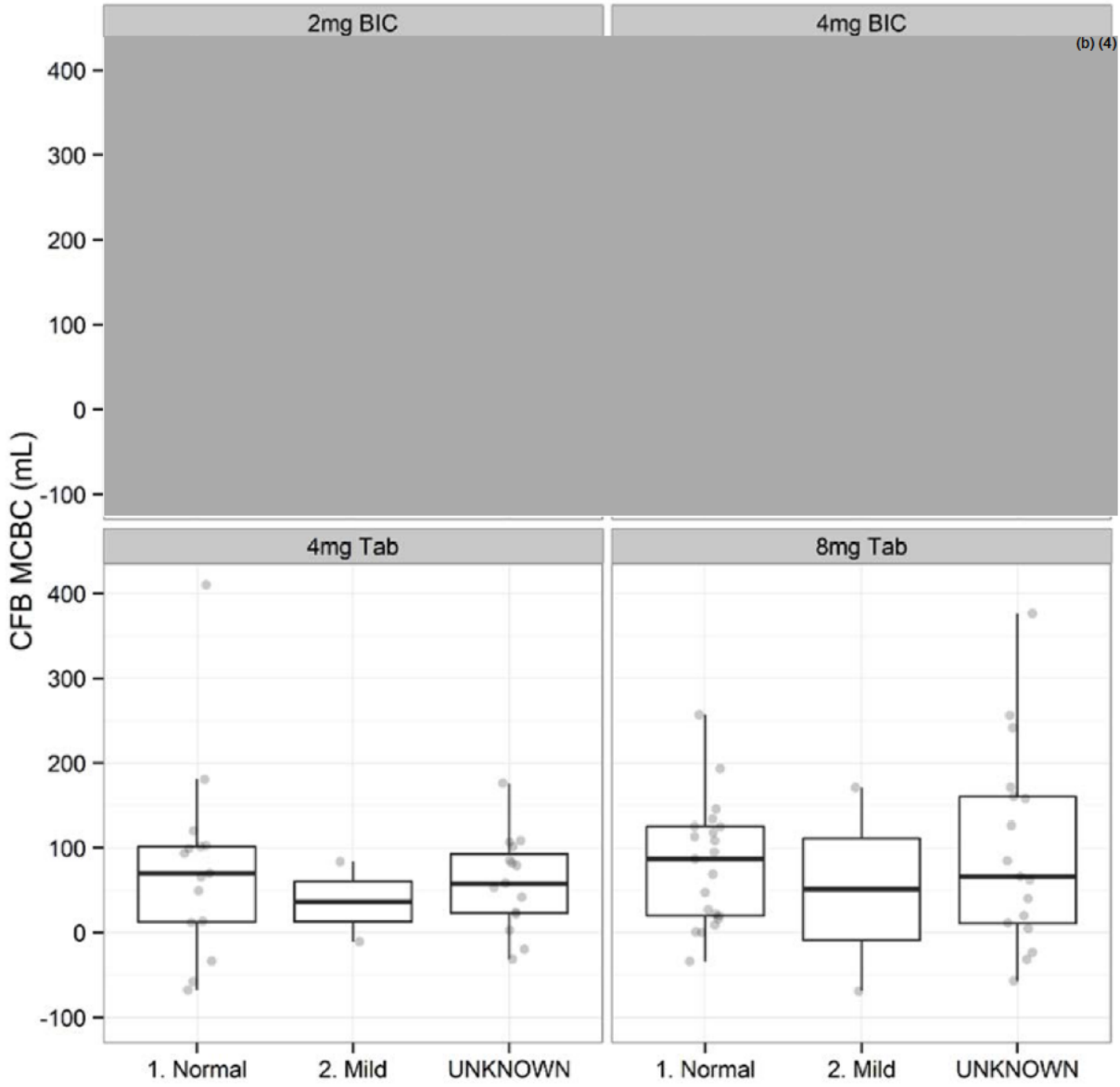
Figure 5: Effect of Renal Impairment on the Estimated 5-HMT Exposures (Cmax,ss) in Study A0221047



Repository step ID CP1:ST-19156059. BIC: Beads in Capsule. Tab: Tablet. Renal function classified based on Clcr calculated using Cockroft-Gault equation for subjects ≥12 years, and eGFR calculated using Schwartz equation for subjects 6-11 years. $C_{max,ss}$ values were estimated based on empirical Bayes estimates following dosing of fesoterodine 4 or 8 mg tablet QD or 2 or 4 mg BIC QD. For each box, median value for $C_{max,ss}$ is designated by a black line in the center of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Jitter dots are actual values to visualize the distribution of each metric in each group.

Source: Figure 2, SDN 1488 (May 19, 2021)

Figure 6: Effect of Renal Impairment on CFB MCBC in Study A0221047



Repository step ID CP1:ST-19156591. BIC: Beads in Capsule. Tab: Tablet. CFB: Change from Baseline. MCBC: Maximum Cystometric Bladder Capacity. Renal function classified based on Clcr calculated using Cockroft-Gault equation for subjects ≥12 years, and eGFR calculated using Schwartz equation for subjects 6-11 years. For each box, median value for CFB MCBC is designated by a black line in the center of the box. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Jitter dots are actual values to visualize the distribution of each metric in each group.

Source: Figure 5, SDN 1488 (May 19, 2021)

Hepatic Impairment

Adult patients with severe hepaic impairment (Child-Pugh C) have not been studied; therefore Toviaz® is not recommended for use in these patients. It should be noted that patients with severe hepatic impairment (Child-Pugh C) were excluded from the Phase 3 study, A0221047. In adult patients with moderate (Child-Pugh B) hepatic impairment, C_{max} and AUC of the active metabolite are increased 1.4- and 2.1-fold,

respectively, as compared to healthy adult subjects. No dose adjustment is recommended in adult patients with mild or moderate hepatic impairment.

As the expected clearance of fesoterodine in pediatric population, including hepatic metabolism and renal excretion, is unlikely to be different than that in adults, no dose adjustment is recommended in pediatric patients with mild or moderate hepatic impairment. Toviaz® is not recommended for use in pediatric patients with severe hepatic impairment (Child-Pugh C).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Drug Interactions

The C_{max} and AUC of 5-HMT increased 2.0- and 2.3-fold, respectively after oral administration of a strong CYP3A4 inhibitor (ketoconazole 200 mg BID for 5 days) with fesoterodine in CYP2D6 EMs. Likewise, in CYP2D6 PMs, C_{max} and AUC of 5-HMT increased 2.1- and 2.5-fold, respectively, during coadministration of ketoconazole 200 mg BID for 5 days. To ensure that 5-HMT exposure would be maintained within a well-tolerated range in patients taking strong CYP3A4 inhibitors, it is recommended to reduce the dose by half to account for the 2-fold increase in 5-HMT exposure in those patients. Thus, for pediatric patients weighing > 35 kg, fesoterodine dose is recommended to be reduced to 4 mg QD in patients taking strong CYP3A4 inhibitors. For pediatric patients with body weight > 25 kg and up to 35 kg, fesoterodine administration is not recommended in patients taking strong CYP3A4 inhibitors.

3.3.5 What formulations were used in the clinical studies of this sNDA?

The studies included in this sNDA evaluated the efficacy, safety, tolerability, and PK of two ER dosage forms, which were included in the pediatric program:

- Fesoterodine 4 and 8 mg tablet dosage form (currently approved for adults with OAB)
- Fesoterodine 2 and 4 mg BIC dosage form

(b) (4)

The formulations used in each clinical study are summarized in Table 11 below.

Table 11: Summary of Fesoterodine Dosage Forms Used in Clinical Studies Supporting Pediatric Formulation Development

Study Number	Clinical Phase	Description	Strength	Formulation Identifier
A0221068	1	(b) (4) (b) (4) (BIC) (BIC) (BIC) Fesoterodine Fumarate ER Tablet	4 mg 4 mg 4 mg 4 mg 4 mg	(b) (4)
A0221069	1	Formulation SR1 (BIC) Formulation SR2 (BIC) Fesoterodine Fumarate ER Tablet	4 mg 4 mg 4 mg	
A0221099	1	Formulation SR3 (BIC) Formulation SR4 (BIC) Fesoterodine Fumarate ER Tablet	4 mg 4 mg 4 mg	
A0221066	2	Fesoterodine Fumarate ER Tablet Fesoterodine Fumarate ER Tablet	4 mg 8 mg	
A0221047	3	Formulation SR4 (BIC) Formulation SR4 (BIC) Fesoterodine Fumarate ER Tablet Fesoterodine Fumarate ER Tablet	2 mg 4 mg 4 mg 8 mg	

Source: Table 2, Module 2.7.1

The quantitative compositions of fesoterodine ER tablets used in clinical studys are summarized in Table 12 below.

Table 12: Summary of Quantitative Compositions of Fesoterodine ER Tablets Used in Clinical Studies

Name of Ingredients	Unit formula	
Formula Identifier	(b) (4) D1005498[a]	D1005499[a]
Strength	4 mg	8 mg
Fesoterodine fumarate	4.0 mg	8.0 mg
Xylitol (b) (4)		(b) (4)
Hypromellose (b) (4)		
Glyceryl behenate		
Talc (b) (4)		
Total Tablet Weight	335.0 mg	335.0 mg

[a] Currently approved commercial drug product

Source: Table 7, Module 2.7.1

Reviewer's Comment: *The Phase 3 trail, A0221047 was conducted using the currently approved commercial formulations. The formulations used in the Phase 2 study, A0221066 is only slightly different in the inactive ingredients compared to the currently approved commercial formulation and is not expected to have clinically meaningful difference.*

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The parent drug fesoterodine is rapidly hydrolyzed to the active metabolite 5-HMT and cannot be detected in plasma; therefore, circulating 5-HMT was measured for PK. Plasma samples were analyzed for 5-HMT concentrations using a validated LC-MS/MS method at [redacted] (b) (4)

Briefly, blood samples were collected into tubes containing sodium heparin. Blood samples were immediately inverted several times to ensure thorough mixing with the anticoagulant and centrifuged at 1700 g for approximately 10 minutes at 4°C. Plasma was harvested and stored at approximately -20°C or lower. 5-HMT and its stable labeled internal standard, [redacted] (b) (4) were extracted from human plasma using a 96-well protein-precipitation extraction procedure. After mixing and centrifugation, the resulting supernatant was transferred to a clean 96-well plate and evaporated to dryness under a stream of nitrogen. The dry residue was reconstituted, vortexed, centrifuged, and analyzed by LC-MS/MS under positive ionization mode. The chromatographic separation was achieved using an Agilent Zorbax Eclipse XDB-Phenyl, 2.1 x 50 mm, 5 µm column and gradient elution. The lower limit of quantitation (LLOQ) for 5-HMT in human plasma was 0.0200 ng/mL with upper limit of quantitation (ULOQ) at 20.0 ng/mL using a plasma sample volume of 100 µL and a 1/x linear regression model. The method validation results are summarized in Table 13 below.

Table 13: Summary of the Bioanalytical Method Validation Results

Report Title	Quantitation of SPM7605 in Human Plasma by Turbo Ion Spray LC/MS/MS	
Pfizer Validation Plan Number	A0229001	
Pfizer Sponsor Location	New York	
Pfizer Principal Contact	Penelope H. Crownover	
Bioanalytical Laboratory	[redacted] (b) (4)	
Bioanalytical Laboratory Project Reference	07020VCJ_PSU_S	
Bioanalytical Laboratory Method Number	07020VCJ_PSU_MR_V2	
Principal Bioanalytical Investigator	[redacted] (b) (4)	
Method Description		
Reference Standard (SPM7605)	Lots JM15062/5PS-4, JM15062/5PS-5, MS17012/2 SS-6, and 090236-QCS	
Internal Standard [redacted] (b) (4)	Lots AC8305RM-4 and AC8305RM-5	
Matrix	Human Plasma	
Anticoagulant	Sodium and Lithium Heparin	
Source of Control Matrix	[redacted] (b) (4)	
Sample Storage Temperature	-20°C	
Extraction Method	Protein Precipitation	
Detection Method	LC/MS/MS	
Sample Aliquot Volume	100 µL	
Regression, Weighting	Linear, 1/concentration	
Quantification	Peak Area Ratios	
Calibration Range	0.02 to 20 ng/mL	
ULOQ	20 ng/mL	
LLOQ	0.02 ng/mL	
QC Sample Concentrations	0.06, 8, 14 and 60 (dilution QC) ng/mL	
Assay Performance - Stability		
Intra-Assay (QC) Sample Statistics	Precision (%CV) ≤2.4%	Accuracy (%RE) -5.7% to 6.2%
Inter-Assay (QC) Sample Statistics	Precision (%CV) ≤4.1%	Accuracy (%RE) -0.7% to 2.3%
Dilution Factors	10-fold	
Stability		
Primary Stock Solution	352 Days at 4 °C for 100 µg/mL in Methanol	
Working Solution	204 Days at 4 °C for 1000 ng/mL in 50:50 Methanol/Water	
Internal Standard Working Solutions	358 Days at 4 °C for 5 ng/mL in 50:50 Methanol/Water	
Frozen Storage Matrix Stability	951 days at -20 °C in sodium heparin human plasma 140 days at -20 °C in lithium heparin human plasma	

Source: Pfizer Validation Study Report (A0229001), Amendment 1

The acceptance criteria and performance of the 5-HMT bioanalytical methods are in compliance with the Agency's *Bioanalytical Method Validation Guidance*. In summary, the method validation and performance of the bioanalytical methods used for this application are acceptable.

4.2 Clinical Studies

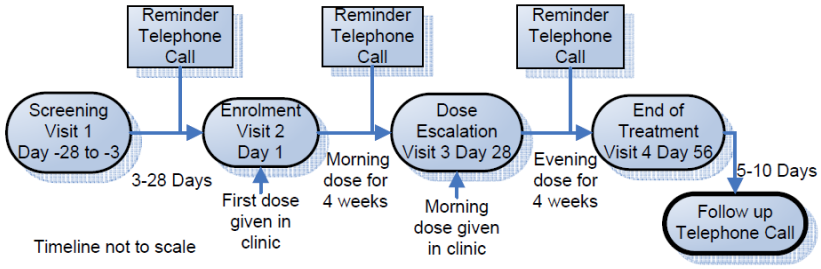
4.2.1 Phase 2 Study (A0221066): Dose Escalating Study of PK, Safety, and Tolerability

Title: An Open-Label, Dose-Escalating Study of the Pharmacokinetics, Safety and Tolerability of Fesoterodine in Pediatric Overactive Bladder Patients Aged 8-17 Years

Primary Objective: To determine the PK of 5-HMT in pediatric OAB subjects aged 8 to 17 years.

Study Design, Treatments, Drug Administration, and Dose Titration Scheme:
This was an 8-week open label, uncontrolled study in male and female subjects with OAB (Figure A-1). A total of 21 pediatric OAB subjects, aged between 9 and 17 years, were enrolled in the study and 20 subjects completed the study. Approximately 50% of the study population were subjects with NDO (11 out of 21 subjects).

Figure A-1: Study Overview



For Weeks 1 to 4, the dose for all subjects was to be fesoterodine 4 mg QD, for Weeks 5 to 8, the study dose was to be escalated to 8 mg QD based on the investigator's assessment of individual subject's tolerability and safety. Subjects were advised to take their medication between 7 and 10 am during Weeks 1 to 4 prior to Visit 3, and between 7 and 10 pm for Weeks 5 to 8 prior to Visit 4. Subjects were instructed to swallow each tablet whole with water regardless of meals.

To limit the blood sampling in pediatric subjects, PK samples at earlier time points post-dose (absorption phase) were collected after dosing in the morning up to Visit 3 (Weeks 1 to 4), and the samples at later time points post-dose (terminal elimination phase) were to be collected after dosing in the evening after Visit 3 up to Visit 4 (Weeks 5 to 8). See the *PK Sampling and Characterization* section below for details.

A bladder diary, noting the number of micturitions/catheterizations events, volume of urine of each micturition or catheterization, urinary urgency and incontinence episodes, was to be completed for 3 consecutive days during the week prior to Visits 2, 3, and 4. Safety parameters included clinical laboratory evaluations, physical examination, vital signs, post-void residual volume (PVR) in subjects who were not performing clean intermittent bladder catheterization (CIC) and the frequency and intensity of adverse events were collected according to the Schedule of Activities (Table A-1).

Table A-1: Schedule of Activities (Study A0221066)

Page 1 of 2

Protocol Activity	Screening[a] Visit 1	Telephone Contact[b]	Enrollment Visit 2	Telephone Contact[b]	Dose-Escalation Visit 3	Telephone Contact[b]	End of Treatment[c] Visit 4	Follow-Up Telephone Contact
	-28 to -3	Prior to enrollment	Week 1 (Day 1)	Prior to next visit	Week 4 (Day 28)[d]	Prior to next visit	Week 8 (Day 56)[d]	Week 9[e]
Informed Consent	X							
Medical History[f]	X							
Physical Examination[g]	X		(X)				X	
Weight & Height[g]	X		(X)					
Vital Signs[h]	X		X[i]		X[i]		X	
Laboratory Assessments								
Blood Chemistry & Hematology	X				X		X	
Urinalysis	X						X	
Urine Drug Screen	X							
Urine/Serum Pregnancy Test[j]	X[k]		X[l]		X[l]		X[l]	
Electrocardiogram (ECG)	X						X	
Post-void residual (PVR) volume	X				X		X	
Study Medication Dispensed			X[m]		X[n, o]			
PK Blood Sampling					X[p]		X[q]	
Subject completed Dosing/Bladder Diaries[r]		X[s]		X		X		
Pharmacogenomics Sample for CYP2D6[t]					X			
Issue Dosing/Bladder Diaries	X[s]		X		X			
Review Dosing/Bladder Diaries			X[s]		X		X	
Adverse Event Monitoring	X ----------X							
Concomitant Medication	X----------X							

Continued

Page 2 of 2

Source: Protocol (Appendix A1)
Abbreviations: PK=pharmacokinetics, IRB=investigational review board, PM=evening, AM=morning
[a]Within 28 days prior to first dose of study medication.
[b]The telephone contact was made prior to the next visit to remind the subject to: complete the bladder diary for 3 consecutive days during the week (7 days) prior to the next visit which could include a weekend, if this was more convenient for the subject; to complete the time of each dose for the 3 days immediately prior to Visits 3 and 4; NOT to take the morning dose of study drug on the day of Visit 3; return diaries and study supplies at each visit; and, of the next appointment date.
[c]End-of-treatment procedures were performed during Visit 4. In the event of an early withdrawal post Visit 2 but prior to Visit 3. PK samples, if possible, were collected at 0.5-2, 2-4, 4-6, 8-10, 10-14, 14-16 hours postdose. In the event of an early withdrawal post Visit 3 but prior to Visit 4, PK samples, if possible, were collected at 8-10, 10-14, 14-16, and 16-20 hours postdose.
[d]Visit window of ±7 days allowed.
[e]Telephone call for follow-up could take place 5-10 days after the last study dose.
[f]Including prior medications, and history of alcohol and tobacco use.
[g]The Screening physical examination, including height and weight, was performed at Entry (Visit 2).
[h]Vital signs included sitting blood pressure, pulse rate and temperature.
[i]Sitting blood pressure, pulse rate, and temperature at predose and 4 hours postdose at Visits 2 and 3.
[j]Females of childbearing potential only. Pregnancy tests could be repeated as per request of IRBs or if required by local regulations.
[k]Serum pregnancy test had to be negative at Screening.
[l]If urine pregnancy test was positive, it was confirmed by a serum pregnancy test.
[m]Instructed subjects to take study medication between 7-10 AM daily until Visit 3, but NOT to take it on the day of Visit 3.
[n]Study drug was given by the study staff on the day of Visit 3.
[o]Instructed subjects to take study medication between 7-10 PM daily starting with the day after this visit date.
[p]Predose and at 0.5-2, 2-4, and 4-6 hours postdose (relative to dose on the morning of Visit 3).
[q]8-10, 10-14, 14-16, and 16-20 hours postdose (relative to dose on the night before Visit 4).
[r]Micturition (Bladder) Bladder Diary had to be completed during the week prior to the next visit for 3 consecutive days (eg, could be done to include a weekend). Dosing diaries had to be completed for the 3 days immediately prior to the next clinic visit.
[s]Bladder diary only.
[t]Had to be collected for subjects who did not have a sufficient laboratory documentation of their CYP2D6 genotype.

Key Inclusion Criteria Related to Clinical Pharmacology:

- Male or female subjects between the ages of 8 and 17 years (age at time of first dose), inclusive;
- A total body weight > 25 kg (55 lb);
- OAB as defined by:
    - Idiopathic or Neurogenic: OAB as defined by symptoms of urinary frequency (≥ 8 micturitions on average per 24 hours) and urgency (defined as a sudden and compelling desire to pass urine which is difficult to defer), with or without urgency incontinence, for at least 6 months prior to enrollment;

    or

    - Subjects with stable neurological disease and urodynamically confirmed detrusor overactivity, who may have required intermittent catheterization for management of urinary drainage;

Key Exclusion Criteria Related to Clinical Pharmacology:
Subjects presenting with any of the following were not to be included in the study:

- Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic (other than neurogenic detrusor overactivity), or allergic (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing) disease that would have impaired their ability to participate reliably in the study, or increased the risk to themselves or others by participating;
- Any condition possibly affecting drug absorption (e.g., gastrectomy);
- Treatment with an investigational drug within 4 weeks or 5 half-lives (whichever was the longer) preceding the first dose of study medication;
- A 12-lead electrocardiogram (ECG) at Screening with clinically significant abnormality;
- Subjects required to take concomitant medications that could have interacted with the PK and/or pharmacodynamics (PD) of fesoterodine, such as:
    - Potent Cytochrome CYP3A4 inhibitors or inducers;
    - Potent CYP2D6 inhibitors;
    - Drugs for treatment of OAB;
    - Drugs with antispasmodic, parasympathetic, or cholinergic effects; or
    - Drugs known to affect lower urinary tract function (eg, desmopressin);

  The above concomitant medications must have had a minimum washout of 1 week, or other period as determined by the investigator prior to the enrollment visit. The subject should have discontinued such agents for at least 3 days prior to beginning the completion of the first bladder diary;

PK Sampling
Blood samples (2 mL each) to provide a minimum of 1.0 mL of plasma for PK analysis of 5-HMT were collected according to the following schedule:

- Visit 3 (Week 4): predose and at 0.5-2, 2-4, and 4-6 hours post-dose (relative to dose on that morning).
- Visit 4 (Week 8): at 8-10, 10-14, 14-16, and 16-20 hours postdose (relative to dose on the previous night).

In the event of an early withdrawal post Visit 2 but prior to Visit 3, PK samples, if possible, were collected at 0.5-2, 2-4, 4-6, 8-10, 10-14, and 14-16 hours post-dose. In the event of an early withdrawal post Visit 3 but prior to Visit 4, PK samples, if possible, were collected at 8-10, 10-14, 14-16, and 16-20 hours post-dose.

PK Analysis Sets
The PK concentration population was defined as all subjects randomized and treated who had at least 1 concentration during the study. Subjects with < 80% compliance with dosing, or concentrations with sampling time deviation > 20% from nominal collection time, were excluded from calculation of summary statistics, but were included in Population PK analysis if dosing on 3 days prior to PK sampling was confirmed and accurate PK sampling was recorded. The PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the PK parameters of primary interest during the study

PK Analysis Endpoints
Model-based PK parameter estimates for K_a, apparent oral clearance, and volume of distribution (V_d) were used to predict the area under the plasma drug concentration versus time curve; a measure of drug exposure (AUC), maximum concentration (C_{max}), time to reach maximum concentration (T_{max}), and half-life in pediatric OAB subjects aged 8 to 17 years.

PK Analysis
The population PK modeling approach was used to analyze the plasma concentration-time data for the fesoterodine 4 mg and 8 mg doses for the estimation of population PK parameters (CL/F, K_a, and V_d) in pediatric subjects in this study. Population mean estimates for the PK parameters were obtained by fitting the PK and variance models to the whole data set of all individuals. The inter-subject variability was estimated and 95% confidence intervals (CIs) were reported for all population parameter estimates. For the residual variability, various models were fitted, including but not restricted to additive and proportional models. Adequacy of model fitting was judged by the objective function as well as goodness of fit plots and parameter precision estimates. Exploratory analyses were performed to investigate the effect of covariates including, but not limited to age, weight, CYP2D6 status, and sex.

Safety Evaluations
Safety was evaluated by the incidence, severity, and relatedness to treatment of all reported and treatment-emergent adverse events and withdrawals from the study due to AEs. Safety assessments included vital signs measurements collected at each visit and medical history and complete physical examination, ECG, and laboratory evaluations (including blood chemistry, hematology, and urinalysis) as defined in the study protocol.

Sample Size Determination:
Based on the adult fesoterodine population PK model, the interindividual variability (IIV) for CL/F was reported to be 26% CV (coefficient of variation) and the IIV for Ka was fixed at 10% CV; the residual variability was reported to be 42.5%. The study design and sample size of 20 subjects was to provide a precise (% standard error [SE] <10%) estimate of clearance (CL).

Bioanalytical Methods:
Samples were analyzed for 5-HMT concentrations at (b) (4) using a validated LC-MS/MS method. Samples were stored at approximately -20°C until analysis and assayed within the 355 days of established stability data generated during validation.

Calibration standard responses were linear over the range of 0.02-20.0 ng/mL; using a weighted ($1/concentration^2$) linear least squares regression. Those samples with concentrations above the upper limits of quantification were adequately diluted into calibration range 0.02-20.0 ng/mL. The LLOQ for 5-HMT was 0.02 ng/mL. Samples with 5-HMT concentrations below the LLOQ are reported as below LLOQ. The between-day assay accuracy, expressed as Percent Relative Error (%RE), for Quality Control (QC) concentrations, 0.06, 0.80, 8.0, to 14.0 ng/mL, ranged between 1.8% and 7.5%. Assay precision, expressed as the between-day percent coefficients of variation (%CV) of the mean estimated concentrations of QC samples, was ≤ 3.3 %.

Disposition of Subjects
A total of 21 subjects were assigned to study treatment and treated (Table A-2). Twenty subjects completed the study, and all enrolled and treated subjects were analyzed for safety (adverse events and laboratory values). One subject was no longer willing to participate and discontinued from the study.

Table A-2: Subject Evaluation Groups

No. of Subjects	Fesoterodine	
	4 mg QD	8 mg QD
Assigned to Study Treatment: 21		
Treated	21	20
Completed	20	20
Discontinued	1	0

Reviewer Comment: *19 subjects and 18 subjects were analyzed for PK from the fesoterodine 4 mg QD group and 8 mg QD group, respectively.*

Demography and Baseline Characteristics

Demographic characteristics and primary diagnoses/durations are summarized in Tables A-3 and A-4, respectively.

Table A-3: Demographic Characteristics

No. of Subjects	Fesoterodine		
	Male N=12	Female N=9	Total N=21
Age (years)			
9 – 12	6	4	10
>12 – 17	6	5	11
Mean (SD)	13.2 (2.6)	13.1 (3.0)	13.1 (2.7)
Range	9 – 17	9 – 17	9 – 17
Race			
White	10	8	18
Black	2	1	3
Weight (kg)			
Mean (SD)	54.0 (18.5)	49.2 (14.5)	51.9 (16.7)
Range	31.8 – 83.9	33.6 – 77.1	31.8 – 83.9
Body Mass Index (kg/m^2)			
Mean (SD)	22.8 (5.8)	23.7 (4.4)	23.2 (5.1)
Range	15.3 – 33.8	18.4 – 31.3	15.3 – 33.8
Height (cm)			
Mean (SD)	153.1 (18.8)	143.1 (12.7)	148.8 (16.9)
Range	118.0 – 188.0	128.0 – 165.0	118.0 – 188.0

Source: Table 13.2.1 and Appendix B2.1
Abbreviations: SD=standard deviation, kg=kilogram, m=meter, N=number of subjects, cm=centimeter, No.=number
Body Mass Index calculated as Weight/(Height/100)^2.

Table A-4: Primary Diagnoses and Durations

	All Subjects N=21
Primary Diagnoses	
Idiopathic overactive bladder[a] (no. of subjects)	10
Duration since onset (years)	
Mean	9.5
Range	4.3 – 17.5
Neurogenic bladder (no. of subjects)	11
Duration since onset (years)	
Mean	9.0
Range	0.6 – 17.4

Source: Table 13.2.2
Abbreviations: N=number of subjects, no.=number, MedDRA=Medical Dictionary for Regulatory Activities, v=version
MedDRA (v13.1) coding dictionary applied.
[a]Also called hypertonic bladder.

Protocol Deviations

There were no significant protocol deviations that would have impacted the safety or the overall outcome of the study.

Concomitant Medication Results

The most frequently used concomitant medications were ibuprofen, docusate, dornase, ferrous sulfate, meropenem, paracetamol, salbutamol, tobramycin, vancomycin, and loratadine.

PK Analyses

The results excluding the concentrations in the three 17-year-old subjects were evaluated to assess the influence of these subjects on the overall interpretation of study results for pediatric subjects across the age

range of 8 years to 16 years and 11 months (Table A-5). As expected, based on the mature development stage across this age range, there was no apparent difference in the PK results when the 17-year-old subjects were included in the analysis dataset. Based on these findings, it was further decided to include these subjects in the population PK analysis dataset to allow robust modeling of 5-HMT population PK.

Table A-5: Plasma 5-HMT Concentration Versus Time Summary, With and Without Inclusion of 17-Year-Old Subjects

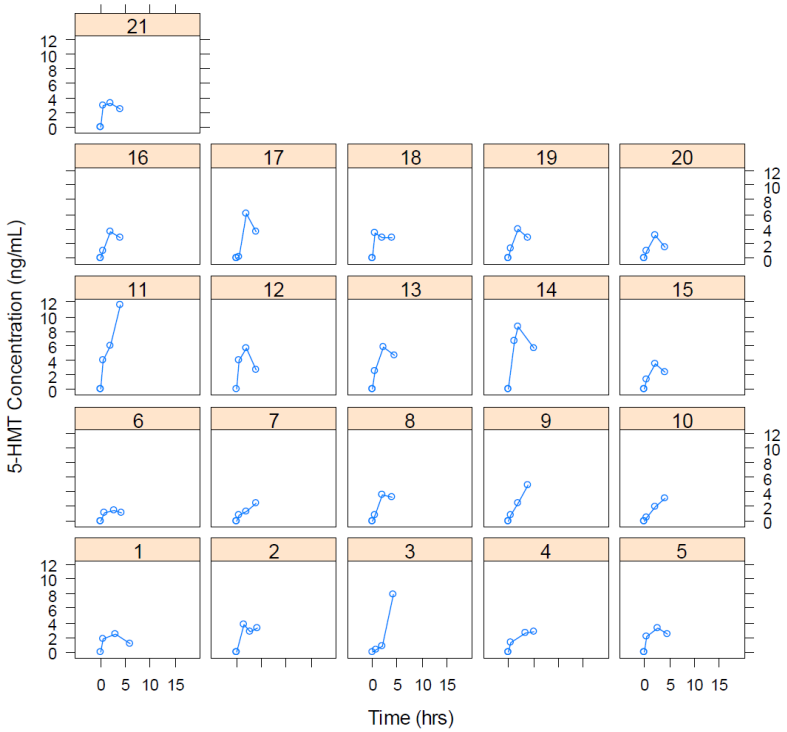
Planned Time Postdose (hours)	N	Plasma 5-HMT Concentration (ng/mL)				
		Mean	%CV	Median	Min	Max
Subjects Aged 8-17 Years Old						
Fesoterodine 4 mg Once Daily						
Visit/hours postdose						
Visit 3/0	19	0.5569	101	0.3170	0.000	1.90
Visit 3/0.5	14	1.722	64	1.350	0.506	3.96
Visit 3/2	14	3.613	56	3.455	0.867	8.60
Visit ¾	16	3.693	71	2.780	1.12	11.6
Fesoterodine 8 mg Once Daily						
Visit 4/8	7	5.179	42	4.750	2.24	7.64
Visit 4/10	12	4.368	46	3.960	1.89	7.77
Visit 4/14	18	2.718	68	2.335	0.000	7.33
Visit 4/16	17	1.568	64	1.280	0.000	3.68
Subjects Aged 8-16 Years Old Only						
Fesoterodine 4 mg Once Daily						
Visit 3/0	17	0.5122	98	0.3170	0.000	1.90
Visit 3/0.5	12	1.752	67	1.350	0.506	3.96
Visit 3/2	13	3.648	58	3.560	0.867	8.60
Visit ¾	14	3.937	69	2.960	1.12	11.6
Fesoterodine 8 mg Once Daily						
Visit 4/8	5	5.182	43	4.750	2.24	7.64
Visit 4/10	10	4.449	47	3.960	1.89	7.77
Visit 4/14	16	2.850	67	2.490	0.000	7.33
Visit 4/16	15	1.642	63	1.310	0.000	3.68

Source: Appendix A14.1
Abbreviations: H=hour; SD=standard deviation; CV=coefficient of variation; Min=minimum, Max=maximum; 5-HMT=5-hydroxy-methyltolterodine; PK=pharmacokinetic, N=Number of observations (non-missing concentrations)
Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 0.0200 ng/mL.
PK samples were collected at Visit 3 (Week 4) and Visit 4 (Week 8).
Subjects with <80% compliance with dosing, or concentrations with sampling time deviation >20% from nominal time were excluded for summary statistics; these data were included in Population PK analysis if dosing on 3 days prior to PK sampling was confirmed and accurate PK sampling was recorded.
Subject (b) (6) and Subject (b) (6) were excluded due to <80% compliance with study drug.

Figure A-2 presents plasma concentrations for fesoterodine 4 mg QD in panel A, and fesoterodine 8 mg QD in panel B.

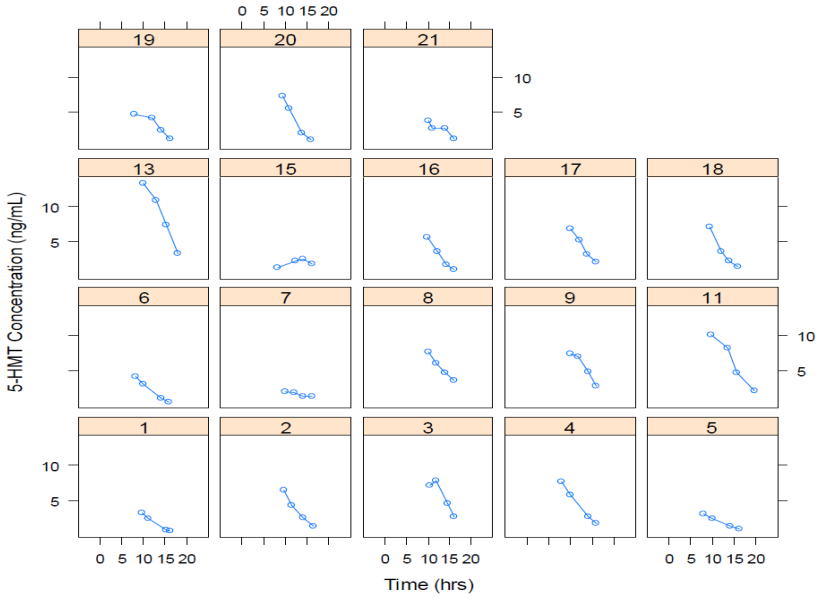
Figure A-2: Plasma 5-HMT Concentrations for
Fesoterodine 4 mg QD (Panel A) and Fesoterodine 8 mg QD (Panel B)

Panel A: Fesoterodine 4 mg QD



For the purposes of plotting data, the dosing time and corresponding concentrations were set to 0 for each subject.

Panel B: Fesoterodine 8 mg QD

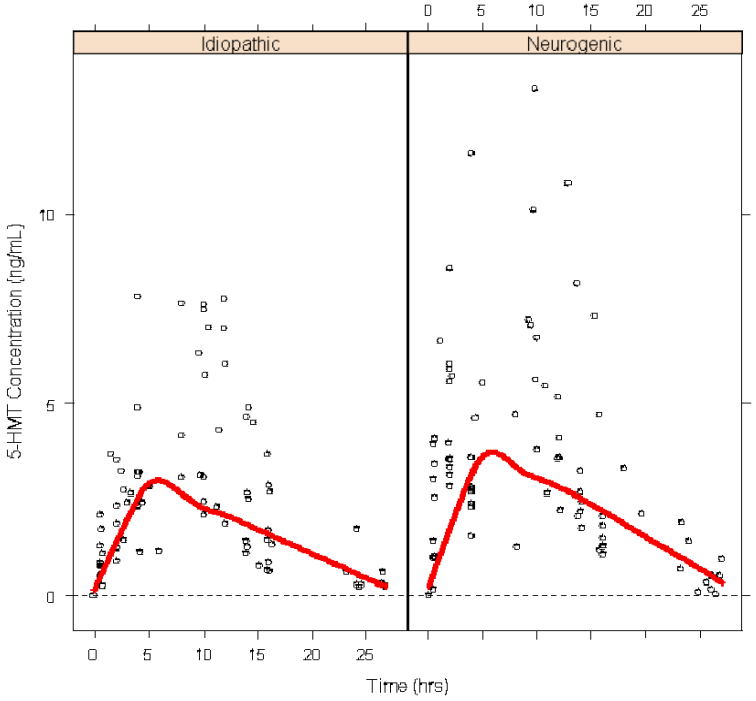


For the purposes of plotting data, the dosing time and corresponding concentrations were set to 0 for each subject.

The 5-HMT concentrations observed in subjects with idiopathic OAB and NDO are shown in Figure A-3. Subjects with NDO did not appear to have any remarkable differences in 5-HMT PK when compared with

subjects with idiopathic OAB. The Applicant believes that somewhat higher exposures in NDO subjects may have been due to the generally lower body weights in this subject group compared with idiopathic subjects.

Figure A-3: Plasma 5-HMT Concentrations Following Once Daily Doses of Fesoterodine 4 mg and 8 mg Administered to Pediatric Subjects With Idiopathic OAB and NDO



The red line indicates Loess (multi-dimensional scatter plot smoother) Local Regression Model.

Population PK analyses were conducted via nonlinear mixed-effects modeling with NONMEM® software; the data were adequately described by a one-compartment model with first-order absorption and elimination. Population PK parameters (CL/F, VC/F) were standardized to a 70 kg person, using the allometric size model. Age or sex were not included as covariates in the final pop PK model due to convergence failure and lack of improvement to explain PK variability. Importantly, the available data from this study contained a small number of children with a limited age range.

The final population PK model provided appropriate description of the data, with the least inter-individual variance values and best precision in point estimates. Goodness-of-fit criteria revealed that the final model was consistent with the observed data and indicated no systematic bias. The point estimates, SEs, and relative standard errors (calculated as standard error/point estimate and expressed as a percentage, %RSE) are presented in Table A-6.

Table A-6: Final Model Parameters

Parameter	Point Estimate	SEE	%RSE	95% CI Lower Limit	95% CI Upper Limit
CL/F (L/h)	86.70	11.4	13.15	63.9	98.1
VC/F (L)	1010.00	222	21.98	566	1232
Ka (1/h)	0.44	0.14	32.95	0.15	0.58
CYP effect on CL	1.33	0.18	13.38	0.97	1.51

Source: Appendix A14.1
Abbreviations: h=hour, SEE= Standard Error of Estimate, CI=confidence interval, CL/F=apparent systemic clearance, VC/F=apparent volume of distribution, Ka=absorption rate constant, CYP=cytochrome
% RSE: Relative Standard Error =100*(SEE/Estimate)

PK modeling & simulation results, based on the adult 5-HMT population PK parameters and allometric scaling of the adult population parameters applied to a distribution of pediatric patients meeting the age and body weight criteria for this study, were used to determine pediatric doses. The actual observed 5-HMT plasma concentrations from this study were in agreement with the simulation results.

Safety Evaluation Results:
There were no deaths, severe adverse events, or permanent withdrawals due to AEs reported. One subject receiving fesoterodine 8 mg QD experienced an severe adverse event that resulted in temporary discontinuation of study treatment. A total of 8 subjects receiving fesoterodine 4 mg QD and 13 subjects receiving fesoterodine 8 mg QD reported adverse events (all causalities). The treatment related adverse events that occurred were 1 adverse event each of dry mouth (mild), constipation (moderate), dry eyes (mild), and vision blurred (moderate), and 2 adverse events of mild nausea and mild residual urine volume increased (increased PVR volume).

Conclusions:

- Clearance of 5-HMT appeared to be similar in pediatric patients compared to adults when allometrically scaled by patient weight.
- Administration of fesoterodine 4 mg QD and 8 mg QD doses to pediatric patients of ages 8 to 17 years with body weight > 25 kg provided steady-state plasma 5-HMT exposures similar to those in adults.
- There were no deaths or permanent discontinuations due to adverse events in this study; there was one severe adverse event of constipation during treatment with fesoterodine 8 mg QD resulting in hospitalization and temporary discontinuation of study treatment. Based on the safety results, fesoterodine treatment was well tolerated by pediatric patients, and there were no significant safety issues.

4.2.2 Phase 3 Study (A0221047): Phase 3, Efficacy, Safety, PK, and Tolerability Study

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

Primary Objectives:

- To determine the safety and efficacy of fesoterodine 4 mg and 8 mg 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.

Secondary PK Objectives:

- Determine the steady-state population PK of 5-HMT following fesoterodine 4 mg and 8 mg once daily treatment in pediatric NDO subjects with weight >25 kg.
- Determine the steady-state population PK of 5-HMT following treatment with 2 doses of fesoterodine 2 mg and 4 mg once daily in pediatric NDO subjects.

Study design

This was a Phase 3, randomized, open-label study to evaluate the efficacy, safety, PK, and tolerability of fesoterodine in participants aged 6 to 17 years with symptoms of NDO. Participants must have had a stable neurological disease and clinically- or urodynamically-demonstrated NDO with no history of indwelling catheter within 4 weeks prior to study participation, no history of autonomic dysreflexia, and no clinically significant UTI at screening. Participants not requiring intermittent catheterization who had a post-void residual volume >20 mL, as determined by transabdominal ultrasound immediately after urination, were excluded.

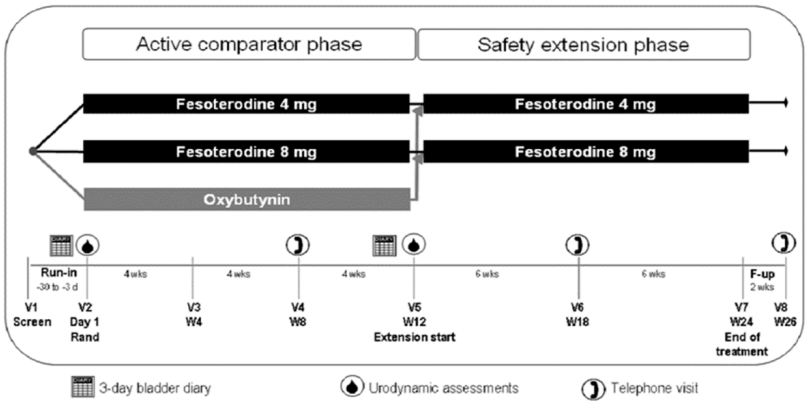
The study included 2 weight cohorts (Cohort 1 included participants > 25 kg dosed with fesoterodine 4 and 8 mg (commercial) ER tablets or oxybutynin XL; Cohort 2 included participants ≤ 25 kg dosed with fesoterodine 2 and 4 mg SR BIC) that were analyzed separately.

Reviewer's Comment: *As only the approved 4 and 8 mg ER tablets are subject to this sNDA this review will only focus on Cohort 1 of this study.*

At baseline, participants in Cohort 1 were randomized in a 1:1:1 ratio to one of 3 treatment arms: fesoterodine 4 or 8 mg or oxybutynin. Subjects swallowed 1 tablet each day without chewing. Subjects took their first dose of study medication in the clinic, to ensure correct dosing and tablet swallowing ability. Subjects in Cohort 1 (weight >25 kg) randomized to oxybutynin received oxybutynin XL tablets at a starting dose in accordance with approved pediatric labeling and accepted practice (e.g., oxybutynin XL 5 mg QD). Dose optimization was achieved by either up or down titration in 5-mg increments on an approximately weekly basis to achieve a balance of efficacy and tolerability. All subjects should have achieved a minimum total daily dose of oxybutynin XL 10 mg by the end of the dose adjustment period at Week 4. The maximum dose used in this study did not exceed the recommended dose consistent with approved pediatric labeling and accepted practice.

After 12 weeks, at the end of the Active Comparator Phase, participants in the oxybutynin treatment arm were allocated by the investigator to fesoterodine 4 or 8 mg tablets for the 12-week Safety Extension Phase.

Figure A-4: Study Design Schematic - Cohort 1



Source: Appendix 16.1.1, Protocol Section 3
Note: The first week of the fesoterodine 8 mg group was at a dose of 4 mg each day, for the Active Comparator Phase and for those subjects changing from oxybutynin to the Safety Extension Phase.

Table A-7: Study Design Schematic - Cohort 1

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										

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
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			
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 (>25 kg subjects) will not be required to provide PK samples. In the event of subject withdrawing early from the active comparator/efficacy 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/efficacy 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 (>25 kg) 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/capsule 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).

PK data from pediatric participants in this study were combined with pediatrics from the Phase 2 study (A0221066) using population PK analysis. The results of this analysis and the effects of covariates, including body weight, CYP2D6 genotype, race, dose, and formulation on 5-HMT plasma concentrations are presented in Section 4.2.1. E-R analysis was also performed using data from this study (A0221047) to investigate the relationship between the post-hoc estimates of 5-HMT exposures and the primary efficacy endpoint of MCBC in pediatric participants. The results of this analysis are presented in Section 4.2.2.

Prohibited Concomitant Medications

Strong CYP3A4 inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the study, as well as medications capable of inducing CYP3A4 enzyme metabolism were prohibited.

PK Analyses and Sampling

At Visit 3 (Week 4), blood samples (2 ml each) to provide approximately 1 mL of plasma for the analysis of 5-HMT were collected. A maximum of three (3) PK blood samples were collected from each subject assigned to receive fesoterodine treatment. Sampling times for the PK samples were determined on an individual subject basis as follows:

- If the dose was administered at the clinic, a blood sample would be obtained just prior to dose administration. If the dose was taken up to 3 hours before coming to the clinic, a blood sample would be obtained just after arrival at the clinic.
- One blood sample was obtained from each subject at about 5 hours (4-6 hrs) post-dose.
- When it was possible for a subject to remain at the clinic, a blood sample could be drawn 8-10 hours after dose administration.

Bioanalysis

Samples was analyzed for 5-HMT using a validated LC-MS/MS method.

PK Results

The observed plasma concentrations of 5-HMT in fesoterodine-treated subjects in Cohort 1 increased as the dose increased from 4 mg QD to 8 mg QD.

Table A-8: Summary of PK Concentrations - PK Concentration Analysis Set - Cohort 1

		Feso 4mg							
Visit*	Planned Time Post Dose	N	NALQ	Mean	SD	CV(%)	Median	Min	Max
4	0 H	10	10	1.930	2.5305	131	0.7960	0.363	8.320
	3 H	24	24	6.603	3.3866	51	6.0000	2.160	12.800
	5 H	26	26	5.719	3.5572	62	5.3800	0.072	13.100
	8 H	14	14	3.176	1.6192	51	3.4250	1.080	6.260

		Feso 8mg							
Visit*	Planned Time Post Dose	N	NALQ	Mean	SD	CV(%)	Median	Min	Max
4	0 H	20	20	3.506	3.5874	102	2.2050	0.556	14.100
	3 H	22	22	8.197	4.6670	57	7.5150	1.620	20.400
	5 H	35	35	9.087	4.4627	49	8.1500	2.360	19.500
	8 H	14	14	4.111	1.6010	39	4.5300	1.820	6.340

* Dosing day refers to dosing day of treatment period for crossover studies and dosing study day for parallel group studies.
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
NALQ = Number of observations Above Lower limit of Quantification.
N = Number of observations (non-missing concentrations

In pediatric patients, from 6 years to 17 years of age with NDO weighing 35 kg with CYP2D6 extensive metabolizer status receiving Toviaz® tablets, the mean values of apparent oral clearance (CL/F), volume of distribution (V_d/F) and absorption rate constant (K_a) of 5-HMT are estimated to be approximately 71.6 (6.7) L/hour, 68.1 (29.7) L, and 0.0897 (5.99)/hour, respectively. The T_{max} and half-life of 5-HMT are estimated to be approximately 2.55 h and 7.73 h, respectively. Like adults, the 5-HMT exposures in CYP2D6 poor metabolizers was estimated to be approximately 2-fold higher compared with extensive metabolizers.

The post-hoc estimates of steady-state exposures of 5-HMT in NDO patients weighing greater than 25 kg following Toviaz® 4 mg and 8 mg tablets once daily are summarized in Table A-9.

Table A-9: Summary of geometric mean [%CV] PK parameters for the active metabolite after steady-state dosing of fesoterodine in pediatric patients with NDO, ages 6-17 years weighing > 25 kg

Dosage	N	$C_{max,ss}$ (ng/mL)	$AUC_{tau,ss}$ (ng*h/mL)
4 mg once daily	32	4.88 (48.2)	59.1 (51.7)
8 mg once daily	39	8.47 (41.6)	103 (46.2)

CV = coefficient of variation; $C_{max,ss}$ = steady-state maximum plasma concentration, $AUC_{tau,ss}$ = steady-state area under the concentration time curve over the 24-hour dosing interval, N = number of patients with PK data

Efficacy Results

The primary efficacy endpoint was the mean change from baseline in maximum cystometric bladder capacity (MCBC) at Week 12. Treatment with Toviaz 4 mg or 8 mg resulted in improvements from baseline to Week 12 in the primary efficacy endpoint, MCBC, with numerically higher changes from baseline for Toviaz 8 mg than for Toviaz 4 mg. Results for the primary endpoint MCBC are reported in Table A-10.

Table A-10: Mean Baseline and Change from Baseline to Week 12 for Maximum Cystometric Bladder Capacity (mL) in Pediatric NDO Patients Receiving Toviaz 4 mg or Toviaz 8 mg and Weighing > 25 kg

	Toviaz 4 mg tablet	Toviaz 8 mg tablet
N	41	41
Baseline	195.1	173.3
Change from baseline (95% CI)†	58.1 (28.8, 87.4)	83.4 (54.2, 112.5)

CI = confidence interval

Baseline is defined as the last available measurement prior to the start of treatment.

N is the number of patients who took at least one dose and provided a valid value for MCBC at baseline.

† Least squares mean change and 95% CI are based on an analysis of covariance model with terms for treatment group, baseline maximum cystometric bladder capacity and baseline weight. Last observation carried forward/baseline observation carried forward was used for imputing missing values at Week 12.

Safety Results

Treatment with fesoterodine 4 and 8 mg once daily for 12 weeks and for up to 24 weeks was well tolerated in pediatric subjects with NDO aged 6 to 17 years weighing >25 kg. There were no treatment-related severe adverse events and no deaths. Treatment-related adverse events were mostly of mild to moderate severity.

Refer to Clinical review for more details regarding efficacy and safety assessment.

Reviewer's Comment: *It should be noted that Study A0221109 was also conducted. This was a Phase 3, multi-center, open-label, long-term extension study in Japanese subjects aged 6 to 17 years with NDO who participated in and completed the precedent Study A0221047 (N = 12). The study consisted of a 28-week open-label treatment period followed by a 4-week follow-up period. In addition, subjects in the oxybutynin arm of the precedent Study A0221047 continued the fesoterodine treatment to which they had been assigned in the Safety Extension Phase of Study A0221047 until Week 40 visit in this study, in order to obtain fesoterodine 1-year treatment data. It should be noted that this study was not reviewed in detail by the Clinical Pharmacology review team. The safety assessment is deferred to the Clinical review team.*

4.3 Population PK Analyses

Review Summary

In general, the applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the developed model was used to support the current submission as outlined in Table A-11.

Table A-11: Specific Comments on Applicant's Final Population PK model

Utility of the final model		Reviewer's Comments
Support applicant's proposed pediatric dose regimen	The recommended dose of Toviaz is 4 mg once daily in pediatric patients 6 years of age and older with a body weight 25 to 35 kg.	The statements are acceptable without significant changes. The predicted exposure in certain pediatric patients with body weight 25-35 kg at 8 mg once daily is higher than the maximal observed exposure in adults at the approved dose, which may result in safety issue. In addition, ER analyses for efficacy suggested there will be a small numerical difference in efficacy between 4 mg and 8 mg QD in patients with body 25-35 kg. Therefore, 4 mg QD is recommended for patients with weight 25 to 35 kg. (b) (4) [redacted]
Derive exposure metrics for Exposure-response analyses	AUCss/Cavg	model-predicted

Aims: Characterize the PK of 5-HMT in pediatric subjects with NDO aged 6-17 years and provide individual-level exposure output (concentration profile over time, $C_{avg,ss}$ (average concentration at steady state), Cmax,ss (maximum concentration at steady state), etc.) for some simulations, as well as subsequent exposure-response analyses.

Data: There are two studies included in the analyses: Study A0221047 and Study A0221066. This analysis included 428 PK observations from 142 pediatric subjects aged 6 to 17 years with body weight ranging from 11.7 to 85.0 kg. Baseline covariates are summarized in Table A-12.

Table A-12. Summary of Main Baseline Covariates.

Category	A0221047 Cohort 1	A0221047 Cohort 2	A0221066	Total
Gender (N (%))				
Male	39 (54.9)	23 (46)	12 (57.1)	74 (52.1)
Female	32 (45.1)	27 (54)	9 (42.9)	68 (47.9)
Race (N (%))				
White	35 (49.3)	19 (38)	18 (85.7)	72 (50.7)
Black	2 (2.8)	0 (0)	3 (14.3)	5 (3.5)
Asian	32 (45.1)	31 (62)	0 (0)	63 (44.4)
Other	2 (2.8)	0 (0)	0 (0)	2 (1.4)
CYP2D6 (N (%))				
EM	69 (97.2)	50 (100)	20 (95.2)	139 (97.9)
PM	2 (2.8)	0 (0)	1 (4.8)	3 (2.1)
Drug Formulation (N (%))				
Tab	71 (100)	0 (0)	21 (100)	92 (64.8)
BIC	[redacted]			(b) (4)
AGE (yrs)				
Mean	10.9	7.64	13.1	10.1
SD	2.44	1.82	2.69	3
Median	11	7	13	10
Min	7	6	9	6
Max	16	15	17	17
BWT (kg)				
Mean	42.2	21.2	51.9	36.2
SD	12.9	3.37	16.7	16.1
Median	38	22	47.2	33.6
Min	25.1	11.7	31.8	11.7
Max	85	25	83.9	85

Repository artifact ID FI-4856077.
BIC = Fesoterodine Beads In Capsule. BWT = Body Weight. EM = CYP2D6 Extensive Metabolizer. N = Number of subjects. PM = CYP2D6 Poor Metabolizer. SD = standard deviation. Tab = Fesoterodine tablet.
Number of subjects in this table represents subjects whose at least one PK data was evaluated.

Source: Table 5 in the PopPK report 1068.

PopPK Model: Pediatric PK data from Studies A0221047 and A0221066 across 142 subjects being treated for OAB or NDO was adequately described by a one-compartment model with first-order absorption/elimination and absorption lag time with a fixed allometric relationship of CL/F and Vd/F, where the effect of gender and CYP2D6 metabolizer status on CL/F, the effect of gender on Vd/F, drug formulation on the extent of absorption (i.e., F) were incorporated into the model. Parameter estimates of the final model are shown in Table A-13. The final model was further assessed via goodness-of-fit indicators and prediction performance (e.g., plots, see Figure A-5). This pediatric final model suggested that variability of fesoterodine exposure in pediatric NDO subjects could be explained mainly by body weight, gender, CYP2D6 metabolizer status and drug formulation with sufficient precision and predictive performance, despite limited information caused by the sparse sampling and the relatively small sample size of the NDO pediatric population. The mean values of apparent oral clearance, volume of distribution and absorption rate constant of 5-HMT are estimated to be approximately 72 L/h, 68 L and 0.09 h^{-1}, respectively (See Table A-13). CL/F for subjects with CYP2D6 PM status was estimated to be 0.546 times lower than that for the EM subjects. CL/F and Vd/F for female subjects was estimated to be 0.862 times and 0.634 times lower than that for male subjects, respectively. These two covariate effects in pediatrics are similar to what was found in adults.

Simulations: Using the final population PK model, Clinical Study Simulation (CTS) was performed. In this simulation, it's assumed that drug formulation (tablet (b) (4)) has an impact on the exposure of 5-HMT. This simulation provides the prediction of 5-HMT steady state exposure of 1000 virtual CTS of children that matches the Study A0221047 criteria with targeted dosing regimen. As shown in Figure A-6, model-predicted 5-HMT steady state exposure following 2 and 4 mg BIC QD administration in subjects with body weight ≤ 25 kg or following 4 and 8 mg tablet QD administration in subjects with body weight > 25 kg agree well with the observed data in black dots.

Using the final population PK model, various dosing regimens have been assessed for their performance on achieving the reference Cavg,ss and Cmax,ss (observed in adult OAB program) for a given weight category. As demonstrated in Figure A-7, the median Cmax,ss value for pediatric participants weighing 25-35 kg and receiving 8 mg tablet QD is estimated to be 11.7 ng/mL, which is 2.45 times greater than median $C_{max,ss}$ value estimated in adults receiving 8 mg tablet QD (4.78 ng/mL). In addition, the predicted exposure in certain pediatric patients with body weight 25-35 kg at 8 mg once daily is higher than the maximal observed exposure in adults at the approved dose, which may result in safety issue. This supports moving from a 25 to a 35 kg body-weight threshold by a decrease in 5-HMT exposure, to the point at which it is within the range of exposure ($C_{max,ss}$ and $AUC_{tau,ss}$) in adults receiving the 8 mg tablet QD. (b) (4)

[redacted]

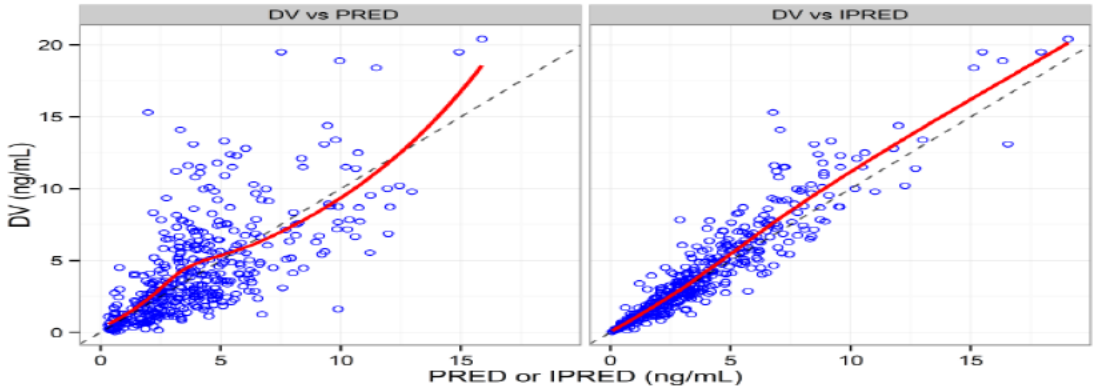
Table A-13: Parameter Estimates of the Final Model.

Parameter [unit]	Estimate (RSE%)	Median [95%CI]
$\theta_{CL/F}$ [L/hr]	71.6 (6.7)	71.4 [63,81.1]
$\theta_{Vd/F}$ [L]	68.1 (29.7)	73.7 [10.8,127]
θ_{ka} [hr^{-1}]	0.0897 (5.99)	0.0902 [0.0804,0.105]
$\theta_{BWT\ on\ CL/F}$	0.75 (FIX)	0.75 [FIX]
$\theta_{BWT\ on\ Vd/F}$	1 (FIX)	1 [FIX]
θ_{ALAG} [hr]	0.285 (45.1)	0.279 [0.00263,0.479]
$\theta_{BIC\ on\ F}$	0.648 (9.38)	0.65 [0.546,0.787]
σ [CV%]	38.1 (8.46)	37.2 [31.6,42.7]
$\theta_{CYP\ on\ CL/F}$	0.546 (12.5)	0.534 [0.343,0.721]
$\theta_{SEX\ on\ CL/F}$	0.862 (8.52)	0.862 [0.716,1.02]
$\theta_{SEX\ on\ Vd/F}$	0.634 (30.6)	0.635 [0.161,1.26]
$\omega_{CL/F}$ [CV%]	46.3 (7.98)	45.4 [37.4,53]
$\omega_{CL/F\ Vd/F}$	0.298 (38.8)	0.275 [-0.095,0.793]
$\omega_{Vd/F}$ [CV%]	114 (19.2)	109 [72,211]
$\omega_{CL/F\ Ka}$	0.0815 (34.3)	0.0686 [0.00161,0.131]
$\omega_{Vd/F\ Ka}$	0.435 (26.7)	0.408 [0.173,0.765]
ω_{Ka} [CV%]	43.2 (16.2)	42 [25.9,59]
OFV	-102.696	
BS success rate (%)	94.3	
Improve step ID	CP1:ST-4701431	CP1:ST-4711175

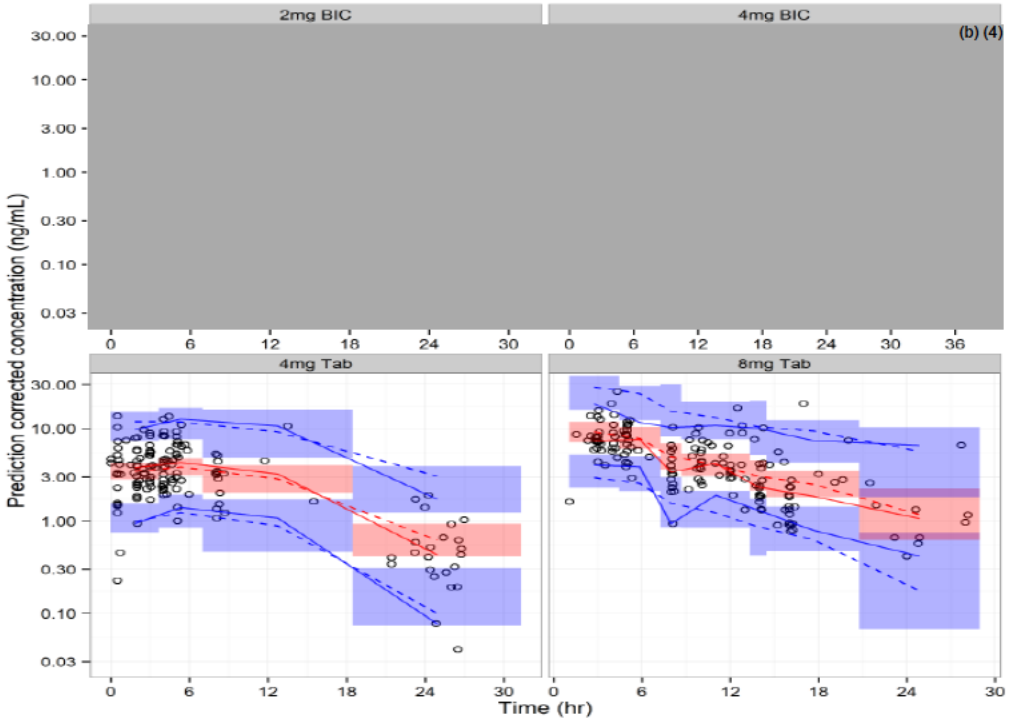
Repository artifact ID FI-4814515.
ALAG = absorption lag time. BIC = Fesoterodine Beads In Capsule. BS = Bootstrap. BWT = Body Weight. CI = Confidence Interval. OFV = objective function value. RSE(%) = Relative Standard Error : 100·(SEE/Estimate). SEE = Standard Error of Estimates. The estimates are for a typical male subject weighing 35 kg with CYP2D6 extensive metabolizer, who receives fesoterodine tablet formulation. SEX on CL/F or V_d/F (female vs. male), CYP on CL/F (CYP2D6 poor metabolizer vs. extensive metabolizer). Median [95%CI] for the population parameters were obtained from the bootstrap.

Source: Table 7 in the PopPK report 1068.

Figure A-5: Goodness-of-fit and Prediction-Corrected Visual Predictive Plots for Final PK Model.



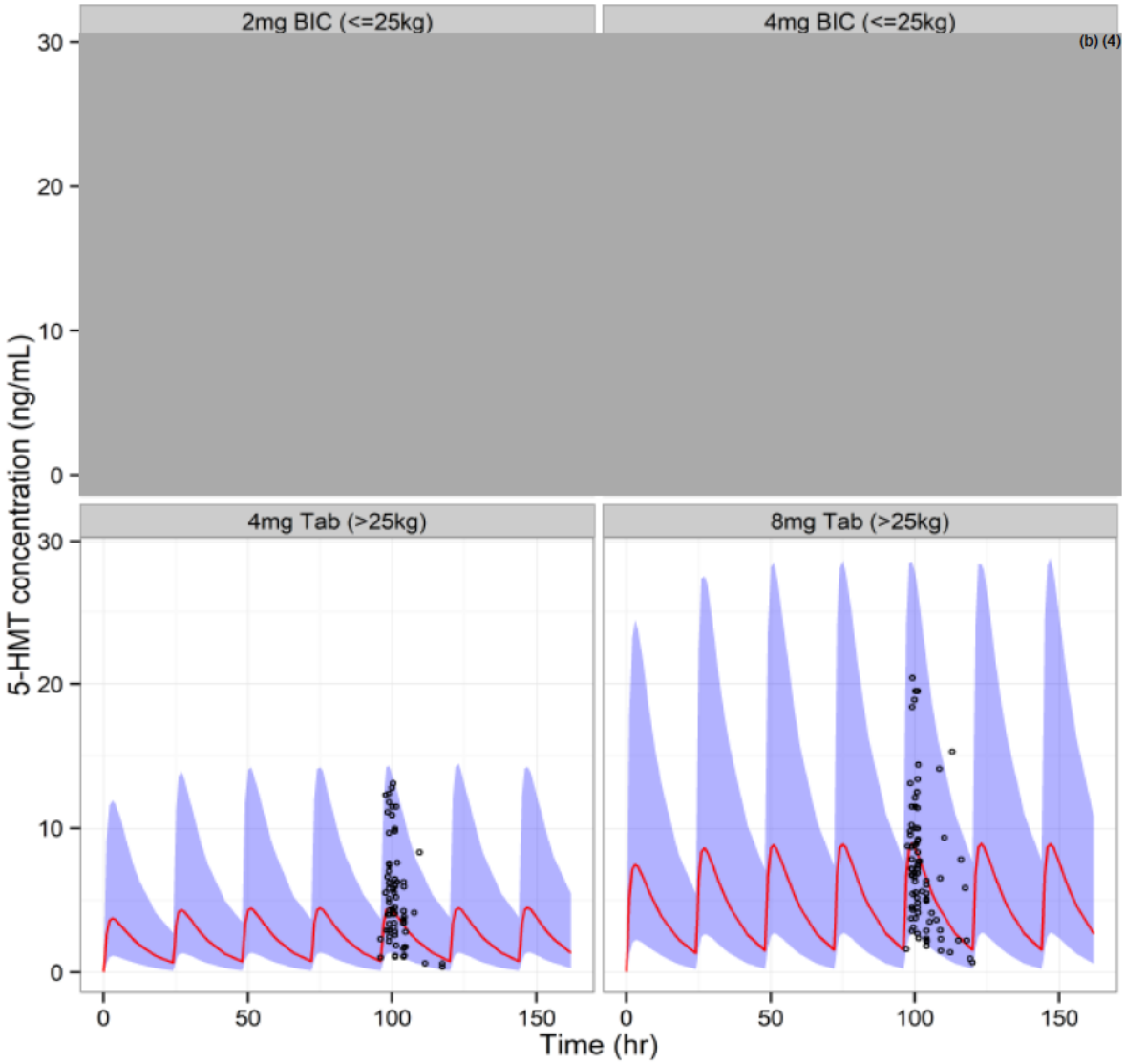
Repository artifact ID FI-4855708.
DV = Observed 5-HMT concentrations. IPRED = Individual predicted concentrations. PRED = Population predicted 5-HMT concentrations. Each red line represents a smoother (loess) line. Each dashed line indicates an identity line (Y = X).



Repository artifact ID FI-4806814.
BIC = Fesoterodine Beads In Capsule. Tab = Fesoterodine tablet. The red lines (blue lines) represent 50 percentile (2.5 and 97.5 percentiles) of observed 5-HMT concentrations. The red dashed lines (blue dashed lines) represent model-predicted 50 percentile (2.5 and 97.5 percentiles) for 5-HMT concentrations. The red areas (blue areas) represent model-predicted 95% confidence intervals of 50 percentile (2.5 and 97.5 percentiles) for 5-HMT concentrations. The open circles indicate individual observed 5-HMT concentration time data.

Source: Figures 2 and A5.6 in the PopPK report 1068.

Figure A-6: Predicted Median (95%CI) 5-HMT Concentration vs. Time Profile for Different Dose Regimens.

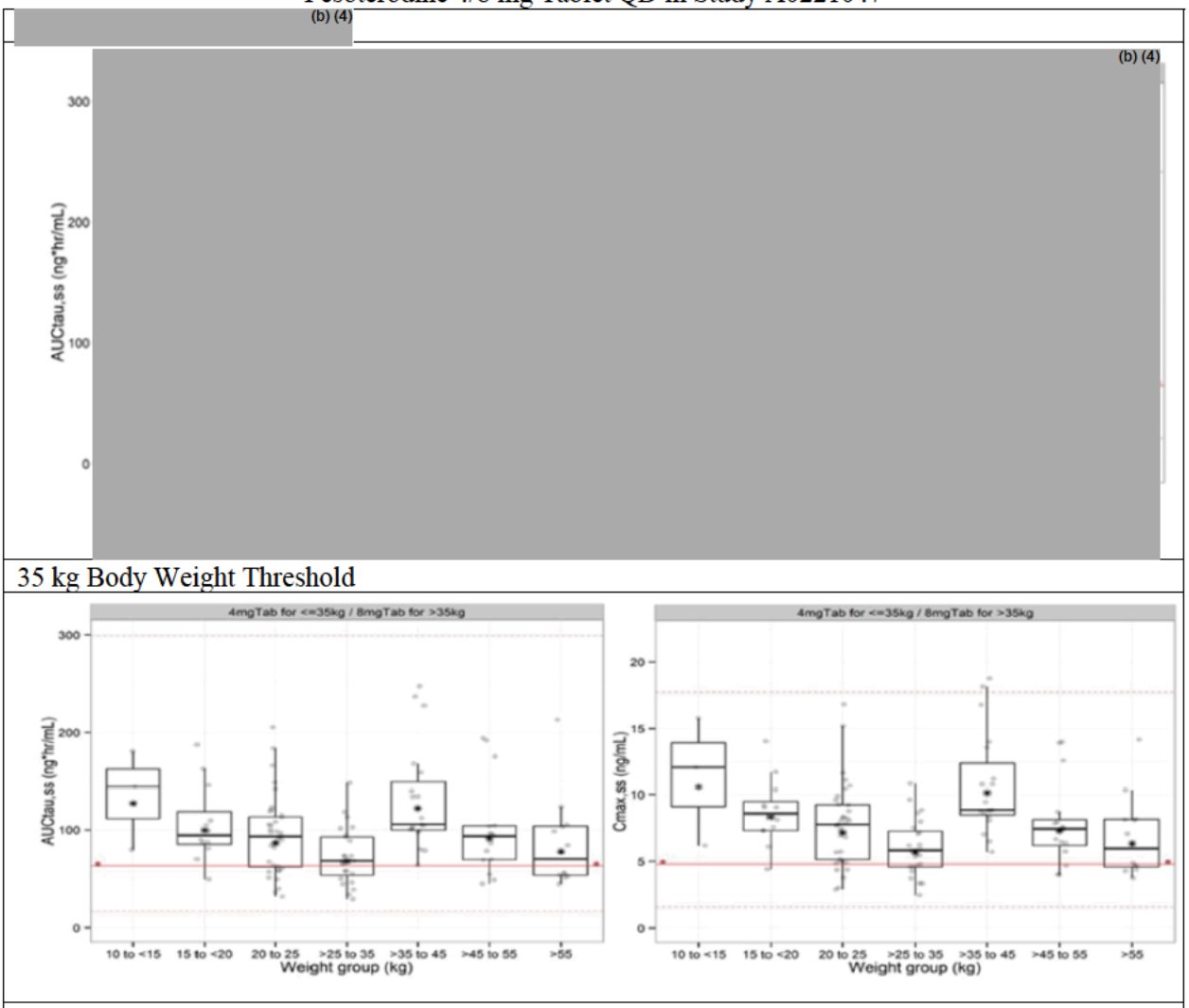


Repository artifact ID FI-4830036.

BIC = Beads in Capsule. Tab = Fesoterodine tablet. TAD = time after dose. The red line shows the population median for 1000 clinical trial simulations, and blue areas represent model-predicted 95% confidence intervals. The open circles are actual observed 5-HMT concentration in Study A0221047 and A0221066. Observed values are plotted as TAD + 96 on x-axis, with TAD > 24 excluded in this figure.

Source: Figure 8 in the PopPK report 1068.

Figure A-7: Distribution of Simulated AUCtau,ss and Cmax,ss Following Administration of Fesoterodine 4/8 mg Tablet QD in Study A0221047



Repository step ID CP1:ST-10291468. For each box, median value for each metric (AUCtau,ss or Cmax,ss) is designated by a black line in the center of the box. Boxes indicate the IQR. Whiskers represent 1.5 IQR. Jitter dots are actual values to visualize the distribution of each metric in each group. The stars in each box represent geometric mean value for each metric. Red solid lines (dotted lines) represent median (range) values for each metric estimated for adults in fesoterodine program, whereas red stars at right and left ends of each figure represent corresponding geometric mean values.

Source: Figure 4 and 5 in Summary of Clinical Pharmacology.

4.4 Exposure Response Analyses

Aim: 1) To investigate the PK/PD relationship between the average concentration at steady-state (Cavg,ss) and change in maximum cystometric capacity (MCC) in pediatric subjects with NDO aged 6-17 years; 2) To assess different dosing regimens based on the PK/PD model.

Data: This analysis included 242 MCC observations at baseline or Week 12 from 121 pediatric subjects aged 6 to 16 years with body weight ranging from 11.7 to 85.0 kg. The baseline characteristics are summarized in Table A-14.

PK/PD Model: The final model was developed from a base Emax model. Age was incorporated into the final model with effects on Base and Emax. The final model structure is shown in Table A-15. The final model parameter estimates are shown in Table A-16. The final model was further assessed via goodness-of-fit indicators and prediction performance (e.g., plots, see Figure A-8). There was no systematic bias or lack of fit observed, suggesting adequacy of the final model. The observed median was generally similar to the simulated median and generally contained within the 95% CI with a slight deviation at higher body weight, indicating that the final model adequately describes the central tendency and the variability of the MCC across all body weights in the NDO pediatric population.

Simulations: Based on the final population PK and PK/PD models established, various dosing regimens have been assessed for their performance on the efficacy for a given weight category. The prediction of change from baseline in MCC by $C_{avg,ss}$ from 1000 simulations for the dosing regimens used in Study A0221047 was performed (see Figure A-9). $C_{avg,ss}$ of approximately 3.5 to 4.0 ng/mL are predicted to provide adequate levels of efficacy (e.g., 55 mL change in MCC), although this model suggested that EC50 may be relatively higher compared to Cavg,ss predicted in this study. In addition, change from baseline in MCC were simulated when subjects received 4 or 8 mg tablet QD in accordance with different body weight thresholds (20 to 35 kg). These simulations suggest that for patients with body weight of 25-35 kg, the dose change from 4 mg QD to 8 mg QD would have minimal impact on predicted median of change from baseline MCC: 46.9 mL at 4 mg QD and 48.3 mL at 8 mg QD. This supports the label statement (b) (4) .

Table A-14: Summary of Main Covariates of Subjects Included in the PK/PD Analysis.

Category	2mg BIC	4mg BIC	4mg Tab	8mg Tab	Total
Gender (N (%))		(b) (4)			
Male			20 (62.5)	19 (48.7)	61 (50.4)
Female			12 (37.5)	20 (51.3)	60 (49.6)
Race (N (%))					
White			14 (43.8)	21 (53.8)	54 (44.6)
Black			2 (6.2)	0 (0)	2 (1.7)
Asian			14 (43.8)	18 (46.2)	62 (51.2)
Other			2 (6.2)	0 (0)	3 (2.5)
CYP2D6 (N (%))					
EM			31 (96.9)	38 (97.4)	119 (98.3)
PM			1 (3.1)	1 (2.6)	2 (1.7)
Drug Formulation (N (%))					
Tab			32 (100)	39 (100)	71 (58.7)
BIC			0 (0)	0 (0)	50 (41.3)
AGE (yrs)					
Mean			10.4	11.3	9.58
SD			2.26	2.54	2.72
Median			10	11	9
Min			7	7	6
Max			15	16	16
BWT (kg)					
Mean			41.2	43	33.5
SD			13.5	12.4	14.4
Median			36	40	28
Min			25.5	25.1	11.7
Max			85	73	85
MCC at Baseline (mL)					
Mean			207	178	165
SD			102	104	94.6
Median			202	161	152
Min			16	20	16
Max			406	451	451

Repository artifact ID FI-6298308.

BIC = Fesoterodine Beads In Capsule. BWT = Body Weight. EM = CYP2D6 Extensive Metabolizer. MCC = Maximum Cystometric Capacity. N = Number of subjects. PM = CYP2D6 Poor Metabolizer. SD = standard deviation. Tab = Fesoterodine tablet.

Source: Table 4 in the PK/PD report 1069.

Table A-15: Final PK/PD Model Structure.

$$MCC_{ij} = \left(BASE_i + \frac{(E_{max,i} - BASE_i) \cdot C_{avg,ss,i}}{EC_{50} + C_{avg,ss,i}}\right) \cdot (1 + \varepsilon_{PRP_{ij}}) + \varepsilon_{ADD_{ij}}$$

$$BASE_i = \theta_{Base} \cdot \left(\frac{AGE_i + 1}{13}\right) \cdot exp(\eta_{BASE_i}) \quad (AGE_i \leq 12)$$

$$BASE_i = \theta_{Base} \cdot exp(\eta_{BASE_i}) \quad (AGE_i > 12)$$

$$EC_{50} = \theta_{EC50}$$

$$E_{max,i} = 30 \cdot (AGE_i + 1) \cdot exp(\eta_{Emax,i}) \quad (AGE_i \leq 12)$$

$$E_{max,i} = 390 \cdot exp(\eta_{Emax,i}) \quad (AGE_i > 12)$$

Where MCC_{ij} denotes the observed MCC for the i^{th} individual at the j^{th} time point (baseline or Week 12), and $BASE_i$, $E_{max,i}$ and AGE_i denote the predicted MCC at baseline, predicted E_{max} and age for the i^{th} individual, respectively. $C_{avg,ss}$ for the i^{th} individual ($C_{avg,ss,i}$) at baseline was set to zero. $\varepsilon_{PRP_{ij}}$ and $\varepsilon_{ADD_{ij}}$ are the proportional and additive residual random errors, respectively, for the i^{th} individual at the j^{th} time point assumed to have zero mean and variance σ^2_{PRP} and σ^2_{ADD}, respectively.

Source: Page 26 in the PK/PD report 1069.

Table A-16: Final PK/PD Model Parameter Estimates.

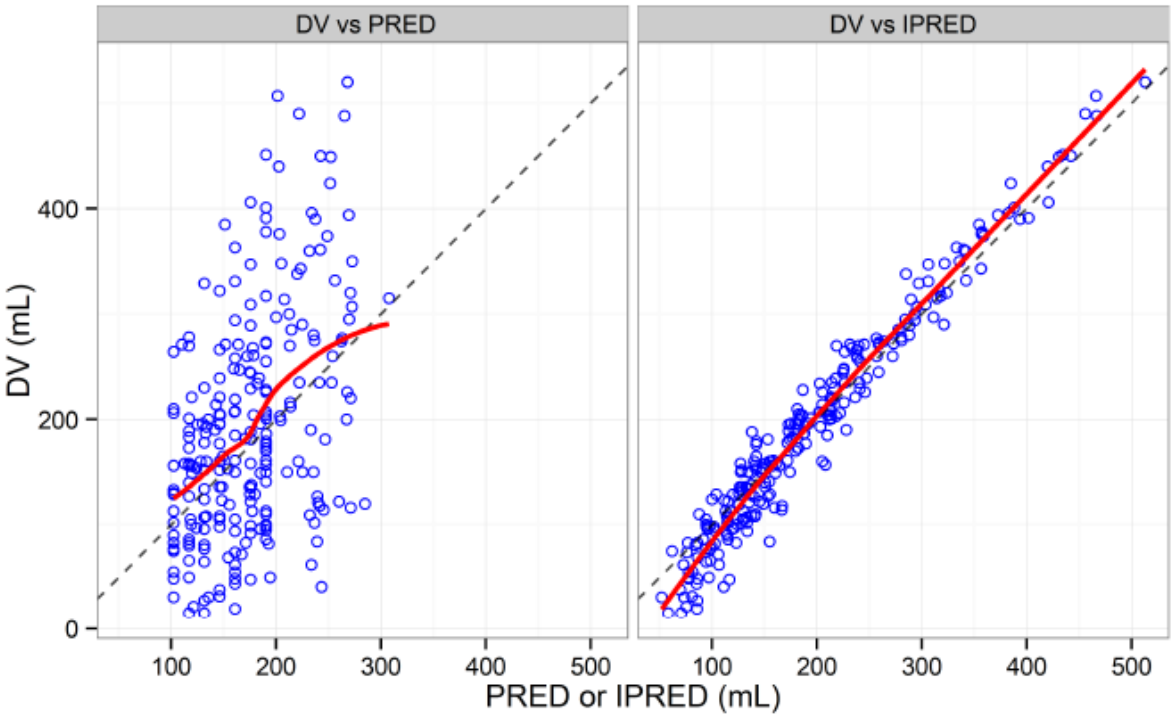
Parameter [unit]	Estimate (RSE%)	Median [95% CI]
θ_{Base} [mL]	190 (5.49)	190 [170,211]
θ_{EC50} [ng/mL]	6.22 (21.8)	6.21 [4.11,10.1]
θ_{Emax} [mL]	390 (FIX)	390 [FIX]
σ_{PRP} [CV%]	7.41 (36.4)	7.25 [0.0729,12.5]
σ_{ADD} [mL]	34.6 (11.1)	34 [26.5,42.1]
ω_{Base} [CV%]	48.8 (7.89)	48.7 [41.2,56.3]
$\omega_{Base\ Emax}$	0.122 (28.3)	0.123 [0.048,0.196]
ω_{Emax} [CV%]	47.1 (14.3)	46.2 [33.7,61.7]
OFV	2326.669	
BS success rate (%)	100	
Improve step ID	CP1:ST-4985771	CP1:ST-5000622

Repository artifact ID FI-5034291.

BS = Bootstrap. CI = Confidence Interval. OFV = objective function value. RSE = Relative Standard Error : 100·(SEE/Estimate). SEE = Standard Error of Estimates. The estimates are for a subject above 12 years old. Median [95%CI] for the population parameters were obtained from the bootstrap. The estimates and RSE values were calculated using R (Improve Step ID: CP1:ST-5023894) directly loading NONMEM output $EST .ext file.

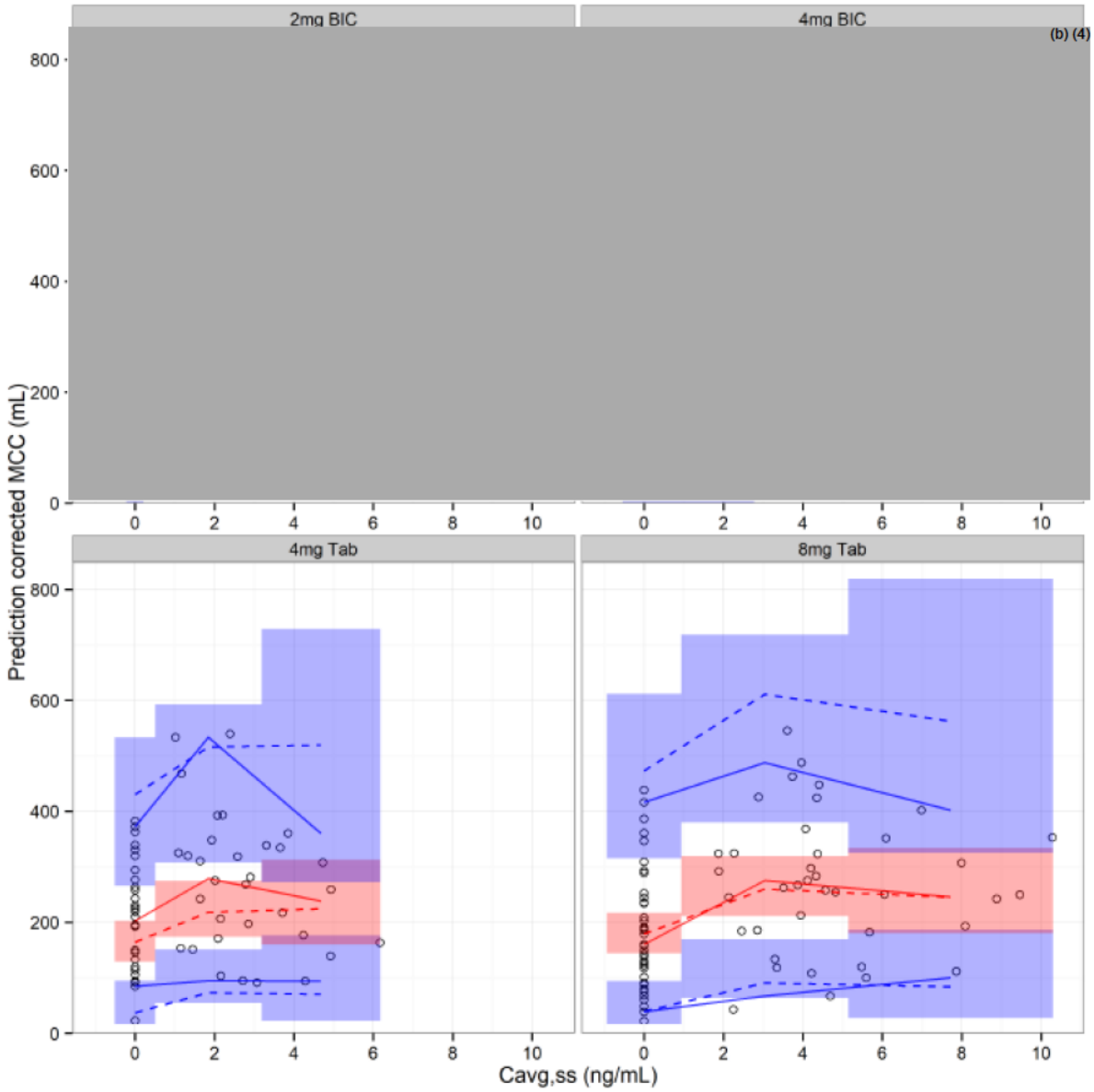
Source: Table 6 in the PK/PD report 1069.

Figure A-8: Final PK/PD Model Assessment Plots.



Repository artifact ID FI-5034679.

DV = Observed MCC. IPRED = Individual predictions. MCC = Maximum Cystometric Capacity. PRED = Population predictions. Each red line represents a smoother (loess) line. Each dashed line indicates an identity line (Y = X).

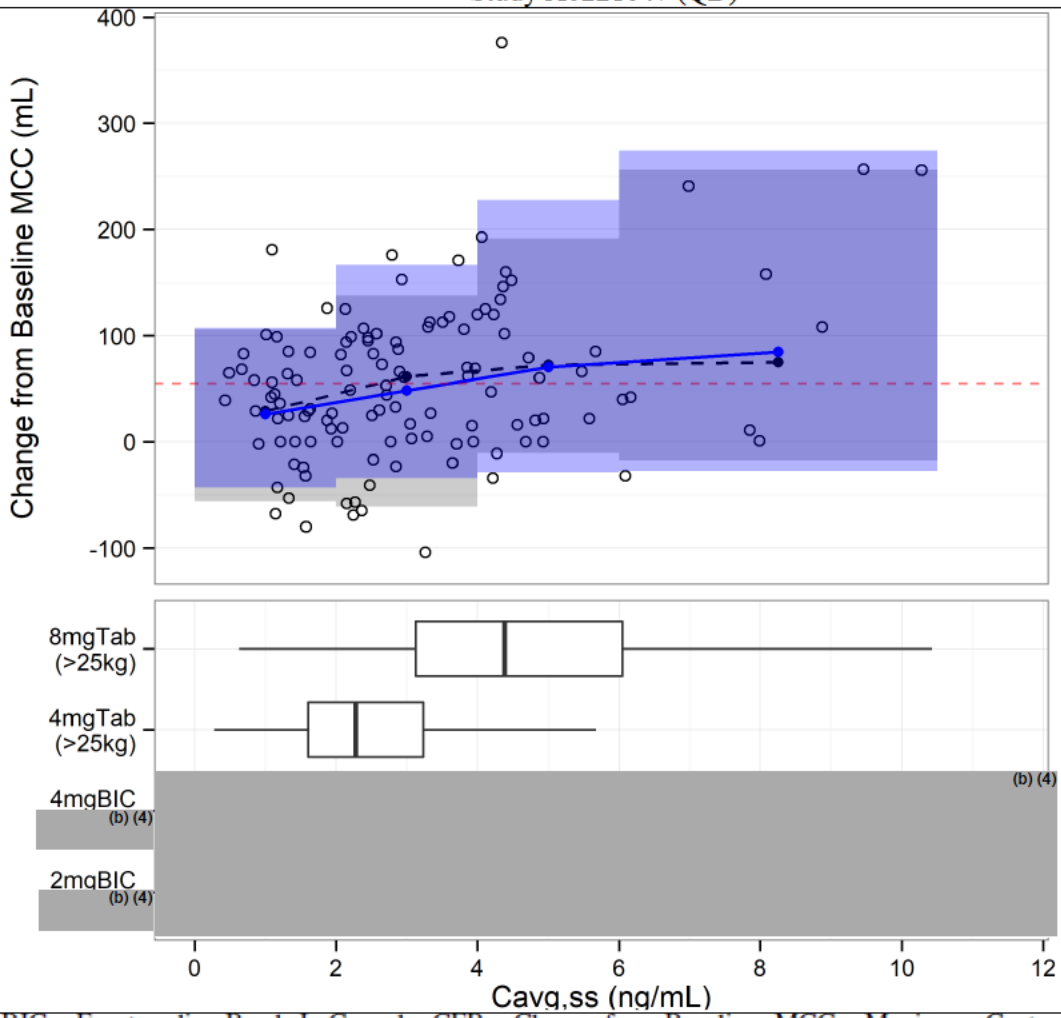


Repository artifact ID FI-5049868.

BIC = Fesoterodine Beads In Capsule. MCC = Maximum Cystometric Capacity. Tab = Fesoterodine tablet. The red lines (blue lines) represent 50 percentile (2.5 and 97.5 percentiles) of observed MCC. The red dashed lines (blue dashed lines) represent model-predicted 50 percentile (2.5 and 97.5 percentiles) for MCC. The red areas (blue areas) represent model-predicted 95% confidence intervals of 50 percentile (2.5 and 97.5 percentiles) for MCC. The open circles indicate individual observed MCC.

Source: Figure A5.6 and Figure 2 in the PK/PD report1069.

Figure A-9: Relationship between Cavg,ss and Simulated CFB MCC for the Dosing Regimens Used in Study A0221047 (QD)



BIC = Fesoterodine Beads In Capsule. CFB = Change from Baseline. MCC = Maximum Cystometric Capacity. QD = Once daily. Tab = Fesoterodine tablet. Virtual subjects were extracted from subjects enrolled in Study A0221047 (121 subjects in each simulation), then simulated individual $C_{avg,ss}$ and MCC 1000 times. Simulated data with $C_{avg,ss}$ > 10.5 ng/mL were excluded from the calculation and the plots. **Top:** The blue line shows the model-predicted population median. The blue area represents model-predicted 90% prediction intervals (5 and 95 percentiles). The dashed black line shows the median of observed data for each bin. The gray area represents 90% confidence intervals (5 and 95 percentiles) of observed data for each bin. The red dashed line represents CFB MCC = 55 mL. The open circles indicate individual observed CFB MCC. **Bottom:** The bold black lines in the boxes represent median for individual simulated $C_{avg,ss}$ in each treatment group while the box edges on the left and the right are the 25th and 75th percentiles, respectively. The whiskers extend up to 1.5 times the interquartile range. Outliers are not plotted in this boxplot.

Source: Figure 3 in the PK/PD report 1069.

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/s/

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