6 October 2022
EMA/CHMP/897876/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Toviaz

International non-proprietary name: fesoterodine

Procedure No. EMEA/H/C/000723/II/0063

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	16 Aug 2021	16 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	20 Sep 2021	22 Sep 2021	☐
☐	CHMP members comments	04 Oct 2021	04 Oct 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Oct 2021	12 Oct 2022	☐
☐	Start of written procedure	12 Oct 2021	12 Oct 2021	☐
☐	Request for supplementary information	14 Oct 2021	14 Oct 2021	☐
☐	Re-start of procedure	03 Jan 2022	03 Jan 2022	
☐	CHMP Rapporteur Assessment Report	07 Feb 2022	08 Feb 2022	☐
☐	CHMP members comments	21 Feb 2022	21 Feb 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	24 Feb 2022	24 Feb 2022	☐
☐	Start of written procedure	01 Mar 2022	01 Mar 2022	☐
☐	Request for supplementary information	03 Mar 2022	03 Mar 2022	☐
☐	Submission of MAH responses	22 Apr 2022	22 Apr 2022	☐
☐	Re-start of procedure	25 Apr 2022	25 Apr 2022	☐
☐	CHMP Rapporteur Assessment Report	30 May 2022	30 May 2022	☐
☐	CHMP members comments	13 Jun 2022	N/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Jun 2022	N/a	☐
☐	Start of written procedure	21 Jun 2022	21 Jun 2022	☐
☐	Request for supplementary information/Opinion	23 Jun 2022	23 Jun 2022	☐
☐	Submission of MAH responses	15 Aug 2022	5 Aug 2022	☐
☐	Re-start of procedure	16 Aug 2022	16 Aug 2022	☐
☐	CHMP Rapporteur Assessment Report	12 Sep 2022	12 Sep 2022	☐
☐	CHMP members comments	26 Sep 2022	N/a	☐
☐	Updated CHMP Rapporteur Assessment Report	29 Sep 2022	N/a	☐
☐	Start of written procedure	4 Oct 2022	4 Oct 2022	☐
☒	Opinion	6 Oct 2022	6 Oct 2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Procedure resources	
Rapporteur:	Concha Prieto Yerro

Declarations

☒The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 30 July 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II and IIIB

C.I.3
Update of sections 4.2, 5.1 and 5.2 of the SmPC with the results from study A0221047, to evaluate the safety and efficacy of fesoterodine in subjects aged 6 to 17 years with neurogenic detrusor overactivity. The change was suggested in the outcome of the EMEA/H/C/000723/P46/030.1.

The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.1.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

This type II variation application is submitted following the request from the CHMP to update the product information including relevant data (from phase 2 and phase 3 completed studies) after the evaluation of the Study A0221047, "A 24-Week Randomized, Open-Label, Study to Evaluate the Safety and Efficacy of Fesoterodine in Subjects Aged 6 to 17 Years With Symptoms of Detrusor Overactivity Associated With a Neurological Condition (Neurogenic Detrusor Overactivity)" within the procedure EMA/H/C/0723/P46/030 in accordance with article 46 of regulation (EC) No 1901/2006, as amended.

The applicant proposes updates to Sections 4.2, 5.1 and 5.2 of the SmPC and claims that these changes do not affect the benefit-risk profile of fesoterodine, which remains favourable when used in accordance with the updated product information.

- The proposed changes are supported by the results of the study A0221047. Data from this study was submitted previously and preliminarily evaluated in the procedure EMEA/H/C/000723/P46 with the conclusion that "*Overall, data from this study are considered positive but limited. Uncertainties are mainly related to posology and long-term safety*".
- No reference is made to the results of the two other completed studies submitted within the procedures EMEA/H/C/000723/P46 (*study A0221066, an open-label, dose escalating study of the pharmacokinetics, safety and tolerability of fesoterodine in paediatric overactive bladder in patients aged 8 to 17 years)* and procedure *EMA/H/C/0723/P46/031 (*A0221109, 'Long-Term Extension Study to Evaluate the Safety of Fesoterodine in Japanese Pediatric Subjects With Symptoms of Detrusor Overactivity Associated With a Neurological Condition (Neurogenic Detrusor Overactivity) Who Have Completed 24 Weeks Treatment in Study A0221047').

Having previously evaluated all three completed studies conducted in paediatric population with NDO, it is considered that the results have no impact on the benefit-risk balance of Toviaz that remains positive.

The popPK model was previously assessed by the Rapporteur and considered appropriate for children with body weight > 25 Kg. It predicts correctly the concentration-time profile for this subgroup. For children weighing less than 25 Kg the model does not describe adequately the paediatric PK data and no predictions can be done based on this model.

Additional data on PK in adults has been taken into the SmPC showing that there are considerable differences on the exposition between paediatric patients with NDO when compared to healthy adults. The MAH was requested to discuss whether this may have any consequence and if so, information valuable for the prescriptor should be reflected in the SmPC. The MAH justified the apparent difference in exposures between paediatric patients with NDO when compared to healthy adults on the basis of the results of one study is not considered representative of the totality of the adult data. The previously established 2-fold difference in 5-HMT exposures between CYP2D6 PMs and EMs in adults supported the dosing recommendations for Toviaz regardless of genotype. Overall, based on these considerations, the comparison of paediatric and adult exposures does not have a clinically relevant consequence or further valuable information for inclusion in the SmPC. This was considered acceptable.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II and IIIB

C.I.3
Update of sections 4.2, 5.1 and 5.2 of the SmPC with the results from study A0221047, to evaluate the safety and efficacy of fesoterodine in subjects aged 6 to 17 years with neurogenic detrusor overactivity as requested in the outcome of EMEA/H/C/000723/P46/030.1.

The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.1.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

This variation concerned the submission of data from Study A0221047, a phase 3, randomized, open-label study to evaluate the safety and efficacy of fesoterodine on paediatric patients aged 6 to 17 with symptoms of detrusor overactivity associated with Neurogenic Detrusor Overactivity (NDO).

Treatment with fesoterodine 4 mg or 8 mg tablets resulted in improvements from baseline in maximum cystometric bladder capacity (MCBC) at Week 12 for paediatric patients > 25 kg, with numerically higher changes from baseline for fesoterodine 8 mg tablets than for fesoterodine 4 mg tablets. Overall, the safety profile in paediatric patients with neurogenic detrusor overactivity was similar to that observed in adults with overactive bladder syndrome.

These safety and efficacy data from Study A0221047 have been described in section 5.1 and 5.2. of the SmPC. No recommendation on posology can be made and uncertainties on the long-term safety remain. Overall, data from this study, although considered positive, remain limited. The safety and efficacy of Toviaz in children aged less than 6 years has not been established.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Results from the Study A0221047 were submitted previously and no new data are presented for this type II variation. Therefore, no additional analysis can be done. The following (section 6) is a copy-paste of the evaluation of the procedure EMEA/H/C/000723/P46:

6. Clinical Efficacy aspects

6.1.1. Clinical study: A0221047

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

Description

This was a Phase 3, randomized, open-label study to primarily evaluate the safety and efficacy of fesoterodine in paediatric subjects aged 6 to 17 years with symptoms of NDO. The study included 2 weight cohorts (Cohort 1 included subjects >25 kg; Cohort 2 included subjects ≤25 kg) that were analysed separately. At baseline, subjects in Cohort 1 were randomized in a 1:1:1 ratio to one of 3 arms: fesoterodine 4 mg or 8 mg or oxybutynin XL at a starting dose in accordance with approved paediatric labelling and accepted practice. After 12 weeks, subjects in the oxybutynin XL arm were allocated by the investigator to fesoterodine 4 mg or 8 mg. At baseline, subjects in Cohort 2 were randomized in a 1:1 ratio to either fesoterodine 2 mg or 4 mg per day. Subjects remained on the same dose for the 12-week efficacy phase and the 12-week safety extension phase.

Methods

Objectives

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

Study design

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

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

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

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

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

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

Study population

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

Treatments

Fesoterodine

Subjects randomized to fesoterodine in Cohort 1 received either 4 or 8 mg fesoterodine prolonged release tablets once daily throughout the initial 12 weeks of the active comparator phase and continued at the same dose during the 12-week safety extension phase. All those assigned to the fesoterodine 8 mg arm started at 4 mg daily for 1 week, and then escalated to 8 mg daily.

Subjects in Cohort 2 were randomized to either 2 or 4 mg fesoterodine BIC capsules once daily throughout the initial 12 weeks of the efficacy phase and continued at the same dose during the 12-week safety extension phase. All those assigned to the fesoterodine 4 mg arm started at 2 mg daily for 1 week and then escalated to 4 mg daily.

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

Oxybutynin

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

Subjects who were unable to tolerate a minimum total dose of oxybutynin XL 10 mg once daily were to be withdrawn. Subjects who withdrew from the oxybutynin treatment arm for reasons of toleration, and who fulfilled all continuation criteria, may have been directly allocated by the investigator to fesoterodine treatment at either 4 or 8 mg per day for the remaining 12-week safety extension phase. All those assigned to the fesoterodine 8 mg arm started at 4 mg daily for 1 week, and then escalated to 8 mg daily.

Efficacy endpoints

Primary efficacy endpoint: Maximum cystometric bladder capacity defined as maximal tolerable cystometric capacity or until voiding/leaking begins or at 40 cm H2O.

Secondary efficacy endpoints:

- Detrusor pressure at maximum bladder capacity
- Presence of involuntary detrusor contraction (IDC)
- Bladder volume at first IDC
- Bladder compliance
- Mean number of micturitions per 24 hours
- Mean number of catheterizations per 24 hours
- Mean number of micturitions and catheterizations combined per 24 hours
- Mean number of incontinence episodes per 24 hours
- Mean urgency episodes per 24 hours if applicable (only for sensate subjects)
- Mean volume voided per micturition
- Mean volume per catheterization
- Mean volume voided per micturition or catheterization

Safety endpoints: Adverse events, including monitoring of targeted AEs (eg. Anticholinergic, CNS, visual). Visual acuity and accommodation, cognitive function, vital signs, urinary tract infections, clinical laboratory evaluations, post-void residual volume, and physical examination.

Pharmacokinetic endpoints: Model-based PK parameter estimates for absorption rate constant (Ka), apparent oral clearance (CL/F), and volume of distribution (Vd) to predict the area under the curve (AUC), maximum concentration (Cmax), time to reach maximum concentration (Tmax), and half-life of

5-HMT. At Visit 3 (Week 4), blood samples were collected from each subject assigned to receive fesoterodine for the analysis of 5-HMT.

Statistical Methods

Cohort 1 Primary Efficacy Analysis

A sample size of 33 evaluable subjects per group is sufficient to give a power of at least 90% to detect a change from baseline of 70 mL in the primary endpoint, maximum cystometric capacity (MCC), when the standard deviation of the change from baseline is 120 mL.

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

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

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

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

- Fesoterodine 4 mg PR versus oxybutynin.
- Fesoterodine 8 mg PR versus oxybutynin.

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

The primary analysis was based on the Cohort 1 Full Analysis Set (FAS). The FAS included all subjects who had been randomized and received at least 1 dose of study medication and had provided baseline primary endpoint data. The Per Protocol Analysis Set (PPAS) included all subjects who had completed the Active Comparator/Efficacy Phase of the study, and who had not violated any of the inclusion/exclusion criteria or deviated from the protocol in a way that could have affected the efficacy outcome of the study.

Cohort 2 Primary Efficacy Analysis

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

The following primary comparisons of interest were assessed:

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

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

The primary analysis was based on the Cohort 2 FAS. For the FAS analysis, a baseline observation carried forward (BOCF) and a last observation carried forward (LOCF) algorithm were used for missing data.

Secondary Efficacy Analyses

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

Pharmacokinetics

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

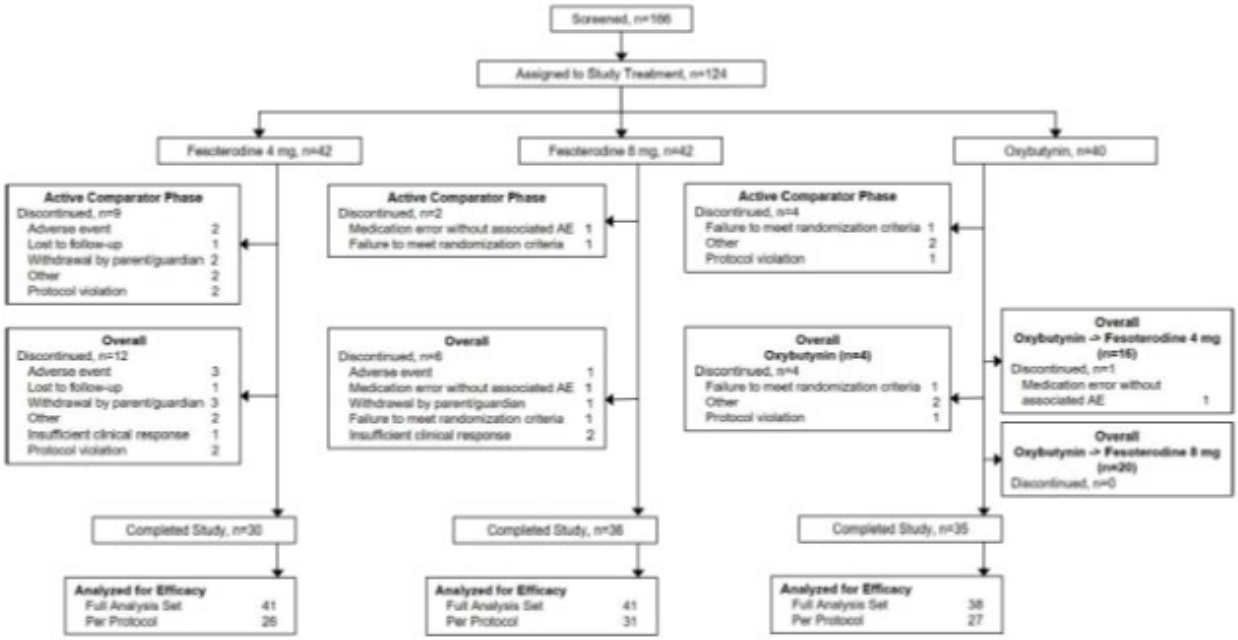
A population PK modeling approach was used to analyze the plasma concentration-time data following fesoterodine administration for the estimation of population PK parameters (apparent oral clearance [CL/F], absorption rate constant [Ka], and volume of distribution [Vd]) of 5-HMT in pediatric subjects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

Results

Recruitment/ Number analysed

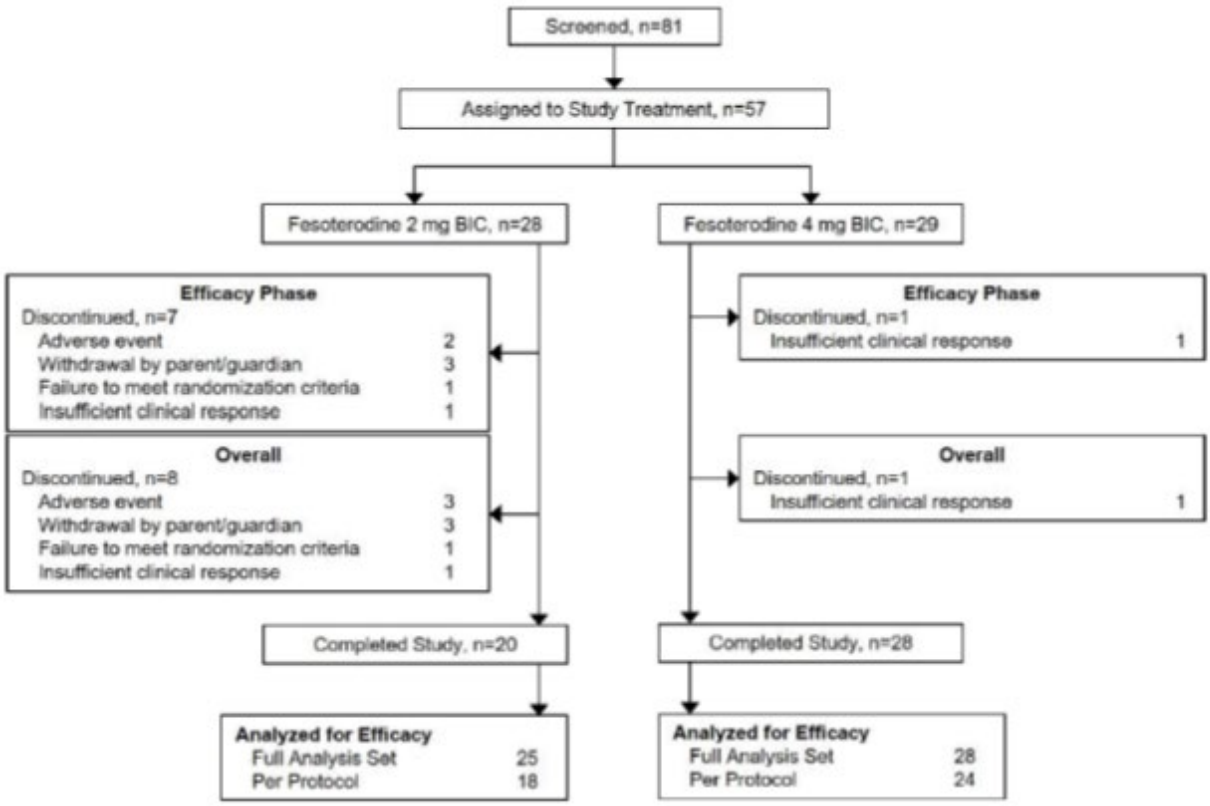
Of 166 subjects screened for Cohort 1, 124 were assigned to treatment: 42 to fesoterodine 4 mg, 42 to fesoterodine 8 mg, and 40 to oxybutynin. For Cohort 1, 101 subjects (81.5%) completed the study. Overall, a higher proportion of subjects randomized to fesoterodine 4 mg discontinued from the study (12 subjects [28.6%]) than those randomized to fesoterodine 8 mg (6 subjects [14.3%]) or oxybutynin (5 of 40 subjects [12.5%], 1 of these discontinued from the study while receiving fesoterodine 4 mg in the Safety Extension Phase), with the most common reasons being AE and withdrawal by parent/guardian. In the Active Comparator Phase, a higher proportion of subjects discontinued from the study in the fesoterodine 4 mg arm (9 subjects [21.4%]) than the fesoterodine 8 mg arm (2 subjects [4.8%]) or the oxybutynin arm (4 subjects [10.0%]).

Figure 1 Disposition Flow Chart – Cohort 1



Of the 81 subjects screened for Cohort 2, 57 were assigned to treatment: 28 to fesoterodine 2 mg BIC and 29 to fesoterodine 4 mg BIC. For Cohort 2, 48 subjects (84.2%) completed the study. Overall, a higher proportion of subjects discontinued from the study in the fesoterodine 2 mg BIC arm (8 subjects [28.6%]) than in the fesoterodine 4 mg BIC arm (1 subject [3.4%]), with the most common reasons being AE and withdrawal by parent/guardian. In the Efficacy Phase, a higher proportion of subjects discontinued the study in the fesoterodine 2 mg BIC arm (7 subjects [25.0%]) than in the fesoterodine 4 mg BIC arm.

Figure 2 Disposition Flow Chart – Cohort 2



Baseline data

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

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

Efficacy results

Primary efficacy endpoint

- For cohort 1 treatment with fesoterodine 4 and 8 mg and oxybutynin resulted in significant increases from baseline to Week 12 in maximum cystometric bladder capacity (p=0.0001, p<0.0001, and p<0.0001, respectively). The 95% Cis for the mean difference for fesoterodine 4 and 8 mg versus oxybutynin included zero.

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

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

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

Per protocol analysis set cohort 1:

		Feso 4mg (N=26)	Feso 8mg (N=31)	Oxybutynin (N=27)
WEEK 12	N	26	31	26
	LS Mean (SE)	73.49 (19.26)	99.03 (17.59)	98.13 (19.18)
	95% CI for mean	(35.16,111.83)	(64.00,134.06)	(59.95,136.30)
	P-value	0.0003	<.0001	<.0001
	Versus Oxybutynin			
	LS Mean (SE)	-24.63 (27.26)	0.90 (26.07)	
	95% CI for mean	(-78.90,29.64)	(-51.01,52.81)	

Descriptive subgroup analysis of Change from Baseline in Maximum Cystometric Bladder Capacity (ml) at Week 12 - Full Analysis Set - Cohort 1

Age Group

			Observed			Change from Baseline					
			N	Mean	St Dev	N	Mean	St Dev	Min	Median	Max
>=6-9	BASELINE	Feso 4mg	15	155.0	71.06						
		Feso 8mg	14	142.1	93.91						
		Oxybutynin	14	141.7	56.20						
	WEEK 12	Feso 4mg	11	199.6	103.45	11	44.9	48.75	-31	53.0	108
		Feso 8mg	14	230.9	97.75	14	88.7	92.93	-32	73.5	256
		Oxybutynin	13	212.2	85.86	13	75.5	101.52	-83	69.0	314
>=10-12	BASELINE	Feso 4mg	14	193.4	104.39						
		Feso 8mg	14	177.9	119.01						
		Oxybutynin	13	158.5	70.64						
	WEEK 12	Feso 4mg	13	267.8	104.57	13	71.0	51.67	-20	82.0	176
		Feso 8mg	13	277.8	112.85	13	91.0	116.98	-57	66.0	376
		Oxybutynin	11	261.7	78.43	11	106.5	86.57	-75	100.0	239
>=13-17	BASELINE	Feso 4mg	12	247.3	111.53						
		Feso 8mg	13	201.8	97.14						
		Oxybutynin	11	199.2	111.67						
	WEEK 12	Feso 4mg	10	330.9	166.04	10	79.4	141.39	-68	74.0	410
		Feso 8mg	13	280.2	139.55	13	78.5	82.44	-69	113.0	193
		Oxybutynin	11	317.8	137.92	11	118.6	147.04	-66	109.0	384

- For Cohort 2, treatment with fesoterodine 2 and 4 mg BIC resulted in increases from baseline to Week 12 in maximum cystometric bladder capacity, with 95% CIs for the mean change from baseline excluding zero.

Table 2 Statistical Analysis of Change from Baseline in Maximum Cystometric Bladder Capacity (ml) at Week 12 – Full Analysis Set – Cohort 2

		Fesoterodine 2mg BIC (N=25)	Fesoterodine 4mg BIC (N=28)
WEEK 12	N	25	28
	LS Mean (SE)	23.49 (10.18)	40.17 (9.62)
	95% CI for mean	(3.03,43.95)	(20.84,59.50)

Baseline is defined as the last available measurement prior to the start of treatment. Based on an ANCOVA model with terms for treatment group,
baseline (for the endpoint being analyzed) and baseline weight.
LOCF/BOCF was used for imputing missing values.
BIC= Beads-in-Capsule.
PFIZER CONFIDENTIAL SDTM Creation: 03MAR2020 (05:17) Source Data: ADUR Output File: ./CDISC/A0221047 CH2/desc infr chg ur mbc 1 c2 Date of Generation: 07APR2020 (09:49)
Table 14.2.2.1b is for Pfizer internal use.

Cohort 1 Secondary efficacy endpoints: of the 11 endpoints that were formally analysed, 7 endpoints demonstrated significant improvements from baseline following treatment with fesoterodine 4 and/or 8 mg (bladder volume at first involuntary detrusor contraction; main number of micturitions per 24 hours [4 mg]; mean number of micturitions or catheterizations combined per 24 hours; mean number of incontinence episodes per 24 hours; mean number or urgency episodes per 24 hours [4 mg]; mean volume per catheterization [8 mg]; mean volume voided per micturition or catheterization [8 mg]), whereas 7 demonstrated significant improvements from baseline following treatment with oxybutynin (bladder compliance; bladder volume at first involuntary detrusor contraction; main number of micturitions per 24 hours; mean number of micturitions or catheterizations combined per 24 hours; mean number of incontinence episodes per 24 hours; mean volume per catheterization; mean volume voided per micturition or catheterization).

Cohort 2 Secondary efficacy endpoints: Of the 11 endpoints that were formally analyzed, 5 endpoints demonstrated improvements from baseline following treatment with fesoterodine 4 mg BIC. Improvements from baseline were not demonstrated for any of the secondary efficacy endpoints following treatment with fesoterodine 2 mg BIC.

Pharmacokinetic results

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

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

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

For Cohort 1, the observed plasma concentrations of 5-HMT in fesoterodine-treated subjects increased proportionally with fesoterodine 4 and 8 mg doses given as the tablet formulation.

The observed mean plasma concentrations of 5-HMT appear to increment in a similar way to the increment between different doses.

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

Safety results

Cohort 1

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

There were no treatment-related SAEs and no deaths. There were few treatment-related TEAEs which were mostly of mild to moderate severity, and similar between both fesoterodine arms.

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

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

Table 3 Treatment-Emergent AEs (All Causalities) – Safety Analysis Set (Active Comparator Phase) – Cohort 1

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

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

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

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

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

During the overall study, there were no TEAEs of seizures or somnolence and no clinically relevant changes were observed in cognitive function or behavior measured by Childhood behavior checklist (CBCL) and Grooved pegboard test (GPT). No clinically relevant changes were observed for visual acuity and accommodation, PVR volume, vital signs, physical examinations, weight, or clinical laboratory tests during the overall study. Increases from baseline in mean pulse rate were observed in the fesoterodine treatment arms, with the highest mean increase being 10.41 bpm at Week 4 of the Active Comparator Phase in the fesoterodine 8 mg arm, but by Week 24 this had trended downwards to a mean increase of 6.54 bpm with a mean increase in the fesoterodine 4 mg arm of only 1.80 bpm. A mild TEAE of Heart rate

increased was reported for 1 subject in the fesoterodine 8 mg arm. The TEAE was considered related to study treatment by the investigator, and the subject completed the study.

Cohort 2

Treatment with fesoterodine 2 and 4 mg BIC once daily for 12 weeks and up to 24 weeks was well tolerated in pediatric NDO subjects with weight ≤25 kg.

There were no treatment-related SAEs and no deaths. There were few treatment-related TEAEs which were of mild to moderate severity, and similar across both fesoterodine arms.

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

In the study overall, the highest incidence of treatment-related TEAEs were gastrointestinal disorders consistent with the known safety profile of antimuscarinic agents when administered to adults.

The only CNS TEAEs reported were headache and dizziness, which are both consistent with the known safety profile in adults. There were no TEAEs of seizures or somnolence, and no clinically relevant changes were observed in cognitive function or behavior measured by Childhood behavior checklist or Grooved pegboard test.

No clinically relevant changes were observed in visual acuity or accommodation, PVR volume, vital signs, physical examination, weight or clinical laboratory tests during the overall study. Increases from baseline in mean pulse rate were observed in both fesoterodine treatment arms at Week 4 in the Efficacy Phase with the highest mean increase being 5.36 bpm in the fesoterodine 4 mg BIC arm, but by Week 24 there was no increase in mean pulse rate in the fesoterodine 2 mg BIC arm and only a mean increase of 4.86 bpm in the fesoterodine 4 mg BIC arm. A mild TEAE of Heart rate increased was reported for 1 subject in the fesoterodine 4 mg BIC arm (CSR 1047). The TEAE was considered not related to study treatment by the investigator, and the subject completed the study. A mild TEAE of Tachycardia that was considered related to study treatment by the investigator was reported for 1 subject in the fesoterodine 2 mg BIC arm. The subject discontinued study drug and discontinued from the study due to the TEAE.

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

6.1.2. Discussion on clinical aspects

At least 25% of clinical problems seen in paediatric urology are the result of neurogenic lesions that affect lower urinary tract function. The principal causes may be classified as acquired or congenital in origin, with the vast majority of bladder dysfunction in children related to neural tube defects, most commonly myelomeningocele. NDO is associated with involuntary contractions of the detrusor muscle, defined as detrusor overactivity, which occur as the bladder fills. This can only be diagnosed with cystometric evaluation.

The outcome of upper urinary tract function is related to detrusor and urethral sphincter function. In dyssynergistic dysfunction, detrusor and urethral sphincter contraction is uncoordinated (detrusor-sphincter dyssynergia) resulting in high intravesical pressures, vesicoureteric reflux, and ultimately renal damage. In children with myelodysplasia, the risk of upper urinary tract deterioration and renal damage approaches 80% when no intervention is instituted. In atonic dysfunction, although a lack of detrusor and

(usually) sphincter activity results in a low pressure bladder generally protecting the urinary tract, incontinence then becomes a problem.

Treatment of NDO in children depends on presentation, underlying cause, and the risk of deterioration in function of both upper and lower urinary tract. Clean intermittent catheterization is first line therapy for bladder emptying in children with areflexic bladders and high postvoid residual urine volume, and may be combined with antimuscarinic therapy in specific populations, e.g., patients with high pressure bladders.

Study 1047 was not placebo-controlled as it would be unethical to delay treatment to patients with NDO, and whilst oxybutynin was included as an active comparator in this study (as the standard of care at the time the study was initiated), no formal comparisons between oxybutynin and fesoterodine were planned as this would have required a prohibitively large study. Therefore, these evaluations are not intended to be utilized to claim superiority or non-inferiority; they are only to be used for an assessment of comparability between fesoterodine and oxybutynin utilizing an estimation approach, and to show internal validity of Cohort 1 of the study as it was conducted.

As the primary objective of the study was to assess changes from baseline within each of the fesoterodine treatment arms, a comparator for the lighter weight cohort (Cohort 2) was not included. The lighter weight cohort was included in the study to obtain efficacy and safety data on the fesoterodine BIC doses studied. In addition, this cohort was prospectively planned as a smaller cohort which was not powered to analyze changes from baseline using formal hypothesis testing; therefore, conclusions are based on mean changes and associated 95% CI.

For the primary efficacy endpoint, treatment with fesoterodine for Cohort 1 and Cohort 2 resulted in improvements (significant for Cohort 1; $p \leq 0.05$) from baseline to Week 12.

Results of the analyses using the Per Protocol Analysis Set or Cohort 1 and for Cohort 2 supported the results of the analyses using the FAS. Results of subgroup analyses defined by age, gender, weight, region, race, ethnicity, and underlying cause of primary diagnosis for change from baseline to Week 12 in the primary endpoint were generally consistent with the overall results.

For Cohort 1, the results of the secondary endpoint analyses generally demonstrated numerical improvements from baseline, supportive of the primary endpoint analysis. There were dose-dependent improvements for the fesoterodine arms, with the results for the fesoterodine 8 mg arm generally comparable to oxybutynin.

For Cohort 2, treatment with fesoterodine 4 mg BIC resulted in improvements (95% Cis excluded zero) from baseline to Week 12 in the urodynamically assessed secondary efficacy endpoints, detrusor pressure at maximum bladder capacity, bladder volume at first, and bladder compliance, and the bladder diary assessed endpoints of mean number of micturitions per 24 hours and mean number of incontinence episodes per 24 hours, for pediatric NDO subjects with weight ≤25 kg. Improvements from baseline were not demonstrated for any of the secondary efficacy endpoints following treatment with fesoterodine 2 mg BIC.

The majority of treatment-related TEAEs were mild or moderate in severity in Cohort 1; there were no serious treatment-related TEAEs. There was no evidence of any adverse effects on vision, post-void residual volume, cognition, behavior or the CNS, other than the well-known effects of headache and dizziness. Small increases in mean sitting heart rate were observed. Antimuscarinic gastrointestinal system effects were consistent with the known safety profile of fesoterodine, but these effects were not more frequent or more severe than those observed with oxybutynin.

Overall, improvements in the primary efficacy endpoint were observed with a statistically significant effect shown with fesoterodine 4 and 8 mg from baseline to week 12. Treatment with fesoterodine 2 and 4 mg

BIC resulted in improvements from baseline to Week 12 in the primary efficacy endpoint. Results of subgroup analyses were generally consistent with the overall results.

Fesoterodine 4 and 8 mg tablets were well tolerated with a safety profile consistent with that observed in adults and no new safety issues were identified. The benefit-risk profile is positive in children with NDO, with the optimum benefit-risk overall being observed at the higher fesoterodine doses.

6.1.3. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. There were higher proportions of patients with TEAEs and discontinuations due to adverse events in the 4 mg dose group compared with the 8 mg group during the active comparator phase in cohort 1, which is not expected. The MAH should comment on that.
2. According to the results of the study, the MAH should elaborate on the dose recommendation by weight.
3. In this regard, the MAH should discuss the relevance of the results, overall and for each age-group, as well as the apparent lack of dose-response relationship in the adolescent´s subgroup.
4. A period of 12 weeks of follow-up is not considered sufficient to define the long-term safety profile in the paediatric NDO population. The MAH should clarify whether it is an ongoing follow-up study.
5. A proposal for the modification of the product information should be provided, including relevant data from both the phase 2 and phase 3 study. The MAH is required to clarify whether the totality of the available clinical data allow extension of indication to the paediatric population and detail their regulatory plans.

6.1.4. MAH responses to Request for supplementary information

On 26 January 2021 the MAH submitted the responses to the requested questions.

Question 1

There were higher proportions of patients with TEAEs and discontinuations due to adverse events in the 4 mg dose group compared with the 8 mg group during the active comparator phase in cohort 1, which is not expected. The MAH should comment on that.

MAH Response

In the active comparator phase in Cohort 1, there were 26 of 42 (62%) participants in the 4 mg fesoterodine group with 1 or more TEAEs compared to 20 of 42 (48%) participants in the 8 mg fesoterodine group and 30 of 40 (75%) participants in the oxybutynin group. The difference between the fesoterodine 4 and 8 mg groups is largely accounted for by the higher number of subjects in the 4 mg fesoterodine group experiencing an infection resulting in a higher incidence of events included in the SOCs Infections and Infestations and Skin and Subcutaneous Tissue Disorders compared to the 8 mg group. Most of these infections were upper respiratory tract infections or urinary tract infections to which paedatric subjects, especially those with neurogenic detrusor overactivity and related neurological disorders, are susceptible. There is no biologically plausible mechanism by which fesoterodine 4 mg could cause a higher rate of infections than fesoterodine 8 mg, and these events are not treatment related. Considering the relatively small sample size, the higher proportion of TEAEs in the 4 mg group that was largely due to a higher incidence of upper respiratory tract infections and urinary tract infections, is most likely to be a chance phenomenon.

The most frequent adverse reactions associated with fesoterodine and other members of the class are anti-muscarinic effects on the gastrointestinal (GI) system. One would expect to see a dose-response effect with a higher incidence of these events in the 8 mg group compared to the 4 mg group, but this was not observed. However, the number of GI events is small, and the events were non-serious and mostly mild or moderate in severity. Therefore, the lack of apparent dose-response both overall and in the anti-muscarinic effects may be a stochastic effect related to the relatively small sample size coupled with the generally well-tolerated nature of fesoterodine.

In the active comparator phase in cohort 1, there were 9 discontinuations in the 4 mg group compared to 2 in the 8 mg group; only 2 of the 9 discontinuations in the 4 mg group were due to adverse events (AEs). One of these 2 AEs was fatigue with restlessness and weight increased, all of moderate severity. He discontinued 4 mg fesoterodine on Day 98 due to the event of fatigue, which was assessed as possibly related to study drug by the investigator. However, fesoterodine is not known to be associated with fatigue. The second AE was epiphysiolysis in the distal tibia that required a leg plaster cast and was not related to fesoterodine according to the investigator.

The other 7 discontinuations in the 4 mg group were not due to AEs (withdrawal by parent/guardian, other, protocol violation, and lost to follow-up). The 4 subjects who withdrew due to protocol violation or "other" were related to protocol deviations, all involving invalid urodynamic assessments at baseline.

One subject in the 8 mg fesoterodine group and 3 subjects in the oxybutynin group were withdrawn due to similar issues with the urodynamic assessment at screening, described as failure to meet the randomisation criteria, other, or protocol violation. All such discontinuations occurred at different sites and across different regions. It is important to consider that this was an open-label study, and participants may have been on anti-muscarinic treatment prior to enrolling in the study

In summary, the higher proportion of patients with discontinuations in the 4 mg group compared to the 8 mg or oxybutynin group was partially due to more patients in that group having issues with urodynamic assessments at screening, and the TEAEs leading to discontinuation are not causally related to fesoterodine. All of these discontinuations were from different sites. The higher proportion of TEAEs in the 4 mg group was largely due to a higher incidence of upper respiratory tract infections and urinary tract infections to which children, particularly those with NDO, are susceptible. Considering the relatively small sample size and generally well-tolerated nature of fesoterodine, this is most likely to be a chance phenomenon.

Question 2

According to the results of the study, the MAH should elaborate on the dose recommendation by weight.

MAH Response

The MAH does not intend to apply for an extension to the indication to include the paediatric population in section 4.1 of the SmPC for the EU and, as such, is not proposing a dose recommendation by weight for the Toviaz MA.

Question 3

In this regard, the MAH should discuss the relevance of the results, overall and for each age group, as well as the apparent lack of dose-response relationship in the adolescent´s subgroup.

MAH Response

Acknowledging the small sample sizes and the lack of stratification by age group at randomisation, for each age group, there was a general increase in the mean changes from baseline as the age groups get older. (This was also observed with the Baseline and Week 12 results). This was observed across all 3 treatment arms in Cohort 1, and is in line with what would be expected given that bladder capacity is expected to increase as age/weight increases. The only exception to this in the observed results is for the fesoterodine 8 mg tablet group, where the change from baseline in MCC for the oldest (adolescent) age group was slightly less than for the other age groups.

This has contributed to an apparent lack of fesoterodine dose response in this age group when assessing the mean changes from baseline. However, in this age group, it is important to note the much lower variability in the fesoterodine 8 mg group (SD=82.44 mL), compared with the fesoterodine 4 mg and the oxybutynin groups (SD=141.39 and 147.04 mL, respectively), and this is also apparent when examining the maximum changes from baseline (410, 193, and 384 mL for fesoterodine 4 mg, fesoterodine 8 mg, and oxybutynin, respectively). Therefore, in this subgroup, the results for the fesoterodine 8 mg group may be somewhat skewed downwards, or conversely, the other groups may be influenced by large maximum outliers (410 and 384 mL for the fesoterodine 4 mg and the oxybutynin groups, respectively). For the median changes from baseline in the adolescent group, there is an apparent dose response for the fesoterodine 4 and 8 mg groups (74.0 and 113.0 mL, respectively). However, given the small sample sizes and the lack of stratification by age group at randomisation, these subgroup analyses are only intended to assess general trends and not to make any definitive conclusions around dose response, and particularly because with small sample sizes the results can be highly influenced by outliers (as observed).

Question 4

A period of 12 weeks of follow-up is not considered sufficient to define the long-term safety profile in the paediatric NDO population. The MAH should clarify whether it is an ongoing follow-up study.

MAH Response

The Paediatric Study Programme for fesoterodine tablets has completed. The final report for Study A0221109, 'Long-Term Extension Study to Evaluate the Safety of Fesoterodine in Japanese Pediatric Subjects With Symptoms of Detrusor Overactivity Associated With a Neurological Condition (Neurogenic Detrusor Overactivity) Who Have Completed 24 Weeks Treatment in Study A0221047,' was submitted to the EMA on 28 September 2020 in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

Question 5

A proposal for the modification of the product information should be provided, including relevant data from both the phase 2 and phase 3 study. The MAH is required to clarify whether the totality of the available clinical data allow extension of indication to the paediatric population and detail their regulatory plans.

MAH Response

The MAH believes that the outcome of its paediatric programme provides enough data to apply for a paediatric indication. However, under Article 8 of the Paediatric Regulation, which applies to fesoterodine, an application for authorisation of a new indication must contain the results of studies performed in accordance with an agreed paediatric investigation plan (or a waiver or a deferral). Since there is no paediatric investigation plan agreed with the EMA for fesoterodine, the MAH is consequently not able to apply for a paediatric indication in the EU.

The MAH proposes to update the product information, via a Type II variation subsequent to the outcome of this procedure (EMA/H/C/0723/P46/030) for fesoterodine to include information on the outcome of the paediatric study programme and to align with QRD version 10.1. Specifically, updates to sections 4 and 5 in the SmPC are under consideration as well as consequential changes to the package leaflet.

6.1.5. Updated overall conclusion

This was a Phase 3, randomized, open-label study to primarily evaluate the safety and efficacy of fesoterodine in paediatric subjects aged 6 to 17 years with symptoms of NDO. Subjects with stable neurological disease and clinically or urodynamically demonstrated neurogenic detrusor overactivity were recruited. Routine clean intermittent catheterization (standard of care) was not required.

The study included 2 weight cohorts (Cohort 1 with subjects >25 kg; Cohort 2 with subjects ≤25 kg) that were analysed separately. At baseline, subjects in Cohort 1 were randomized in a 1:1:1 ratio to one of 3 arms: fesoterodine 4 mg; fesoterodine 8 mg; oxybutynin XL for secondary comparison and assay sensitivity. After 12 weeks, subjects in the oxybutynin XL arm were allocated by the investigator to fesoterodine 4 mg or 8 mg. At baseline, subjects in Cohort 2 were randomized in a 1:1 ratio to either fesoterodine 2 mg or 4 mg per day. Subjects remained on the same dose for the 12-week efficacy phase and the 12-week safety extension phase. No formal statistical hypothesis testing was performed for the cohort 2.

The duration of 12 weeks for the evaluation of efficacy is considered appropriate but for the safety extension phase, a period of 12 additional weeks of follow-up is insufficient to demonstrate long-term safety and 12 months are the recommended duration.

Urodynamic assessment and bladder diary-based outcome measures were established. There were no clinician impression questionnaires or patient-reported outcome measures / quality of life questionnaires for the secondary endpoints.

Overall, improvements in the primary efficacy endpoint (maximum cystometric bladder capacity –MCBC-) were observed with a statistically significant effect shown with fesoterodine 4 and 8 mg from baseline to week 12

Data from the age subgroup analysis (pre-specified subgroups although not stratified at randomization) showed that the differences between 4 mg and 8 mg dose are important for the lower age groups but not so in the group of adolescents. This unexpected result is *justified by the MAH based on the small sample size and differences in variability between age subgroups* In the cohort 2 also the high dose (4 mg BIC-beads-in-capsule-) was more effective in improving MCBC but the mean effect was lower than in all doses

of the cohort 1, and aligned with the effect shown in the subgroup of children 6 to 9 years of age receiving 4 mg in cohort 1.

Regarding the secondary endpoints, some significant improvements from baseline were shown with fesoterodine. Within the urodynamic measures only bladder volume at first involuntary detrusor contractions supports the primary endpoint. Also significant effect in number/volume of micturitions or catheterizations, incontinence or urgency episodes was demonstrated although these measures are not so clearly indicative of improvements in bladder compliance/detrusor contractility. A significant improvement on bladder wall compliance was demonstrated with oxybutynin.

Administration of 2 mg fesoterodine BIC to patients ≤25 kg did not achieve steady-state plasma 5-HMT exposure similar to those in adults receiving 4 mg tablet. Children less than 25 kg bodyweight receiving fesoterodine 4 mg BIC (64.8% relative bioavailability for BIC compared with tablet) had similar 5-HMT concentrations to those over 25 kg receiving fesoterodine 4 mg tablet.

Fesoterodine 4 and 8 mg tablets were well tolerated with a safety profile consistent with that observed in adults, with higher frequencies in infections commonly seen in children, mainly upper respiratory or urinary tract infections to which NDO children are susceptible. There were increases from baseline in mean pulse rate and tachycardia. No TEAEs of seizures or somnolence and no clinically relevant changes were observed in cognitive function or behaviour However, a period of 12 weeks of follow-up is not considered sufficient to define the long-term safety profile in the paediatric NDO population.

Overall, data from this study are considered positive but limited. Uncertainties are mainly related to, posology and long-term safety. The MAH considers that the outcome of the paediatric programme provides enough data to apply for a paediatric indication but notes that this is not possible from a regulatory point of view since an agreed paediatric investigational plan is lacking. They will submit a type II variation application to update the product information with data from the paediatric studies. This is supported. It is foreseen that, in case of positive outcome these changes would apply to sections 5.1 and 5.2 of the SmPC.

7. Changes to the Product Information

As a result of this variation, sections 4.2, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet (PL) is updated accordingly.

In addition, the list of local representatives in the PL is being revised.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

8. Request for supplementary information

8.1. Major objections

None.

8.2. Other concerns

Clinical aspects

1. Some pharmacokinetic data reflected in the SmPC are missing from the clinical study report submitted. The complete information should be provided.
2. The product information should be revised. The extent of the information should be in line with that in adult patients, taking also into account that no paediatric indication is claimed.

9. Assessment of the responses to the request for supplementary information

9.1. Major objections

None.

9.2. Other concerns

Clinical aspects

Question 1 and 2

Assessment of the MAH's response

In response to RSI, on 22 December 2021 the MAH submitted an updated proposal for the Product Information.

A Population Modelling Analysis Report was also submitted to support the data in section 5.2. Following the revision it is considered that the SmPC needs further amendments. The comments are in the product information document.

Conclusion

New amendments are needed on SmPC, please refer to PI.

10. 2nd Request for supplementary information

10.1. Other concerns

Clinical aspects

1- New amendments are needed on SmPC, please refer to PI.

11. Assessment of the responses to the 2nd request for supplementary information

Question 1. New amendments are needed on SmPC, please refer to PI.

MAH's response

The MAH sent the Product information.

Assessment of the MAH's response

The Rapporteur has raised a comment in the SmPC section 5.2, please see the PI attached.

It is observed that there are considerable differences on the exposition between paediatric patients with NDO when compared to healthy adults. Whether this may have any consequence should be discussed by the MAH. If this were the case and the information were considered valuable for the prescriptor, it should be reflected in the SmPC (section 5.2.)

Conclusion

Issue not solved, please see the SmPC attached.

12. 3rd Request for supplementary information

1. It is observed that there are considerable differences on the exposition between paediatric patients with NDO when compared to healthy adults. Whether this may have any consequence should be discussed by the MAH. If this were the case and the information were considered valuable for the prescriptor, it should be reflected in the SmPC (section 5.2.)

13. Assessment of the responses to the 3rd request for supplementary information

On July 2022, the MAH submitted the response to the question 1 in the 3rd RSI and an updated proposal for the Product Information.

MAH response

The pharmacokinetics of festerodine in humans was investigated in several clinical trials in extensive and in poor CYP2D6 metabolizers. Table 4 below summarizes the main pharmacokinetic parameters of 5-HMT, the active metabolite of fesoterodine, in subjects with CYP2D6 extensive metaboliser (EM) and poor metaboliser (PM) genotype. Mean Cmax and AUC of the active metabolite are 1.7 and 2-fold higher, respectively, in CYP2D6 PMs as compared to EMs.

Table 4 Summary of mean ± standard deviation pharmacokinetic parameters of the active metabolite 5-HMT after a single dose of 8 mg fesoterodine across Phase 1 studies in healthy adult subjects

	SP567 (n=11)	SP564 (n=12)	SP684 (n=11)	SP683 (n=8)
		CYP2D6 EMs		
C_{max} (ng/mL)	4.69±2.02	4.76±2.05	3.29±1.55	5.99±3.36
$AUC_{(0-tz)}$ [ng/mL*h)	51.73±13.85	61.55±27.56	40.77±15.74	70.93±36.15
	SP567 (n=0)	SP564 (n=6)	SP684 (n=6)	SP683 (n=4)
		CYP2D6 PMs		
C_{max} (ng/mL]	-	10.27±3.76	6.93±2.86	6.90±1.61
$AUC_{(0-tz)}$ (ng/mL*h)	-	133.14±48.75	92.55±30.42	88.54±12.78

Source: Module 2.7.2, Section 2.7.2.3.4 of Original MAA

The steady-state exposures of 5-HMT in healthy adult subjects following fesoterodine 4 mg and 8 mg tablets once daily are summarised in Table 5

Table 5 Summary of geometric mean [% CV] pharmacokinetic parameters for the active metabolite 5-HMT after steady-state dosing of fesoterodine in healthy adult subjects, 18 years to 50 years of age

Dosage/Formulation	N	$C_{max,ss}$ (ng/mL)	$AUC_{tau,ss}$ (ng*h/mL)
4 mg QD/tablet	6	1.71 (74.9)	16.39 (69.8)
8 mg QD/tablet	6	4.66 (43.3)	46.51 (46.8)

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

A comprehensive review of 5-HMT exposures in adults with CYP2D6 EM and PM genotype status across various Phase 1 studies in comparison with the exposures in pediatric patients summarized in the proposed label (Table 6) suggests that pediatric exposures are within the range of adult exposures observed at the 8 mg dose level.

Table 6 Summary of geometric mean [% CV] pharmacokinetic parameters for the active metabolite 5-HMT after steady-state dosing of fesoterodine in paediatric patients with NDO or OAB, weighing >25 kg

Age	Dosage/Formulation	N	$C_{max,ss}$ (ng/mL)	$AUC_{tau,ss}$ (ng*h/mL)
6 to 17 years (patients with NDO)	4 mg QD/tablet	32	4.88 (48.2)	59.1 (51.7)
	8 mg QD/tablet	39	8.47 (41.6)	103 (46.2)
8 to 17 years (patients with NDO or OAB)	8 mg QD/tablet[1]	21	7.15 (39.5)	86.4 (44.0)

[1] dosing was initiated at 4 mg QD for 4 weeks and escalated to 8 mg QD for the next 4 weeks.
Abbreviations: $AUC_{tau,ss}$ = steady-state area under the concentration time curve over the 24 hour dosing interval; $C_{max,ss}$ = steady-state maximum plasma concentration; CV = coefficient of variation; N = number of patients with PK data; QD = once daily.

In conclusion, the apparent difference in exposures between paediatric patients with NDO when compared to healthy adults on the basis of the results of one study (Table 5) is not considered representative of the totality of the adult data shown in Table 4. The previously established 2-fold difference in 5-HMT exposures between CYP2D6 PMs and EMs in adults supported the dosing recommendations for Toviaz regardless of genotype. Overall, based on these considerations, the comparison of paediatric and adult exposures does not have a clinically relevant consequence or further valuable information for inclusion in the SmPC (section 5.2.) for the prescriber.

Assessment of the MAH's response

The applicant has provided the requested clarification, which is considered acceptable. Additional supporting data have been included in section 5.2. of the SmPC.

Issue solved

14. Attachments

1. Product Information (changes highlighted)