U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	022030 (S-019)
Drug Name:	Toviaz (fesoterodine fumarate) extended release tablets
Indication(s):	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 6 years of age and older with a body weight > 25 kg
Applicant:	Pfizer Inc.
Date(s):	Submission Date: 12/18/2020 PDUFA Due Date: 6/18/2021
Review Priority:	Standard
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Keywords: neurogenic detrusor overactivity (NDO), change from baseline

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

Toviaz (fesoterodine fumarate) 4 mg and 8 mg tablets are currently approved under NDA 022030 for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency in adults. A Written Request (WR) for the use of Toviaz in treatment of neurogenic detrusor overactivity (NDO) was issued on 14 November 2011 and the WR requirements were subsequently amended on 19 May 2014, 03 October 2016, and 27 June 2019, respectively.

In this submission, the Applicant submitted the safety and efficacy data from Study A0221047 to partially fulfill the WR and to seek approval of Toviaz for the treatment of NDO in pediatric patients at least 6 years old with a body weight greater than 25 kg. This review is to evaluate from a statistical perspective if the submitted data supports this claim.

Study A0221047 enrolled two cohorts (Cohort 1: subjects ≤ 25 kg; Cohort 2: subjects > 25 kg). For Cohort 1, this study was a multinational, multicenter, randomized, open-label, parallel group, phase 3 study with a 12-week, 3-arm (Toviaz 4 mg, Toviaz 8 mg, and active comparator oxybutynin extended release [XL]) efficacy phase followed by a 12-week, 2-arm (Toviaz 4 mg and 8 mg) safety extension phase. The current review focuses on Cohort 1 only.

The primary efficacy endpoint was the change from baseline in maximum cystometric bladder capacity (MCBC) at Week 12. Change from baseline to Week 12 in MCBC for each treatment group was estimated using an analysis of covariance (ANCOVA) including terms for treatment group, baseline MCBC and baseline weight. The least square (LS) mean change from baseline for each treatment group, and its corresponding standard error (SE) and 95% confidence intervals (CIs) were reported. The lower bound of the two-sided 95% CI was assessed to see if it excluded 0. Selected secondary efficacy endpoints based on urodynamics and patient diaries were also evaluated in a similar way as the primary efficacy endpoint.

For Cohort 1 of Study A0221047, the estimated increase in MCBC from baseline to Week 12 was 58.1 mL (95% CI: 28.8 to 87.4) for Toviaz 4 mg tablet and 83.4 mL (95% CI: 54.2 to 112.5) for Toviaz 8 mg tablet, respectively.

The study demonstrated that there is a clinical benefit of Toviaz in the treatment of NDO in pediatric subjects at least 6 years old with a body weight greater than 25 kg.

2 INTRODUCTION

2.1 Overview

Toviaz (fesoterodine fumarate), a muscarinic receptor antagonist, was approved for the treatment of overactive bladder (OAB) in adults in the United States on October 31, 2008 (NDA 022030). Under the Pediatric Research Equality Act (PREA), as stated in the original approval letter for Toviaz, FDA required that the Applicant, Pfizer Inc., conduct a deferred pediatric study for the treatment of OAB in the pediatric patients with neurological disease. On 14 November 2011, FDA issued the Pediatric Written Request (PWR) requesting Pfizer to conduct clinical studies in the pediatric population with neurogenic detrusor overactivity (NDO). The PWR was subsequently amended on 19 May 2014, 03 October 2016, and 27 June 2019.

The current supplementary New Drug Application (sNDA 022030) under review is to seek approval of Toviaz for the treatment of NDO in pediatric subjects at least 6 years old and weighing greater than 25 kg. The statistical review for this sNDA is based on a 24-week, open-label, randomized study, A0221047 (hereafter in this review will be referred to as Study 1047), which included 2 cohorts as follows:

- Cohort 1: pediatric subjects with NDO weighing > 25 kg who received either Toviaz tablets 4 mg, Toviaz tablets 8 mg, or oxybutynin extended release (XL) tablets 5mg, once daily, randomized 1:1:1 in 3 parallel-arm groups.
- Cohort 2: pediatric subjects with NDO weighing ≤ 25 kg who received a new fesoterodine beads-in-capsule (BIC) formulation 2 mg or fesoterodine BIC 4 mg once daily, randomized 1:1 in 2 parallel-arm groups

(b) (4)

, the current statistical review will only review the data from Cohort 1 of Study 1047 to evaluate if the submitted Cohort 1 data support the indication for the treatment of NDO in pediatric patients 6 years of age and older with a body weight > 25 kg.

Key design features of Study 1047 for Cohort 1 are outlined in Table 1.

Table 1. Summary of Key Features of Study 1047 - Cohort 1

Study Number (No. of Sites)	Phase and Design	Treatment Period	# of Subjects per Arm	Subject Population
A0221047 (65)	Phase 3, open label, 3-arm, randomized, active comparator, parallel group, multicenter, multinational	Efficacy: 12 weeks Safety Extension: 12 weeks	Enrolled/Treated (N = 124): Toviaz 4mg: 42 Toviaz 8mg: 42 Oxybutynin XL: 40	Pediatric patients with NDO aged 6 – 17 years old weighing > 25 kg

2.2 Data Sources

The study protocol, reports, data, and additional information for Study 1047 were submitted electronically, and are located in the Electronic Document Room at \\CDSESUB1\evsprod\NDA022030 under submission dates 12/18/2020, 2/15/2021, 4/8/2021, and 5/3/2021.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant submitted both tabulation data and analysis data for the study. Data sets were complete and documented. Statistical analysis programs were submitted.

The statistical analyses of efficacy endpoints were carried out following the pre-specified statistical analysis plan. Additional analysis results were submitted in response to FDA's information requests.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

For Cohort 1, Study 1047 was a randomized, open-label, active comparator, parallel group study. The study consisted of 2 phases (Active Comparator Phase and Safety Extension Phase): a 12-week 3-arm efficacy phase (Toviaz 4 mg and 8 mg and an active comparator [oxybutynin XL]), followed by a 12-week, 2-arm extension phase without the active comparator. Subjects were randomized in a 1:1:1 ratio to one of 3 arms: Toviaz 4, 8 mg or oxybutynin XL. Randomization was stratified by the subject's body weight (≤50 kg, >50 kg). In the Safety Extension Phase, subjects in the oxybutynin arm were allocated by the investigator to Toviaz 4 or 8 mg tablet. Subjects in either of the Toviaz arms in the efficacy phase continued the same dose to which they had been randomized.

The primary efficacy endpoint was change from baseline to Week 12 in maximum cystometric bladder capacity (MCBC), defined as maximal tolerable cytometric capacity or until voiding/leaking begins or at 40 cm H_2O.

Secondary efficacy endpoints of clinical interest were as follows.

Changes from baseline to Week 12 in:

1. Detrusor pressure at maximum bladder capacity
2. Presence of involuntary detrusor contractions (IDC)
3. Bladder volume at first IDC
4. Bladder compliance
5. Mean number of incontinence episodes per 24 hours
6. Mean volume per catheterization
7. Maximum catheterized urine volume per 24 hours

Of these seven secondary efficacy endpoints of clinical interest, six (#1 - #6) were pre-specified in the protocol. The diary-based secondary efficacy endpoint, "maximum catheterized urine volume per 24 hours", was an endpoint that was not pre-specified in the protocol and requested

by FDA given its clinical importance. The Applicant submitted the requested analysis results for it on 8 April 2021.

3.2.2 Subject Populations and Analysis Datasets

The Applicant pre-defined the following analysis sets for Cohort 1 analysis in the study protocol.

Full Analysis Set (FAS): All subjects who had been randomized and received at least 1 dose of study medication and have provided baseline primary endpoint data.

Per Protocol Analysis Set (PPAS): 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.

Active Comparator Safety Set: All subjects who received at least 1 dose of study medication during the Active Comparator Phase.

Safety Extension Phase: All subjects who received at least 1 dose of study medication during the Safety Extension Phase.

Overall Study Safety Set: All subjects who were randomized to Toviaz during the Active Comparator Phase and received at least 1 dose of study medication during both phases of the study.

Per protocol, the primary efficacy analyses are based on the Cohort 1 FAS (N = 120). The subject disposition, demographics and baseline characteristics in this review are summarized based on the Overall Study Safety Set (hereafter in this review will be referred to as Safety Set) (N = 124).

3.2.3 Statistical Methodologies

The efficacy evaluation of Toviaz was based on the mean change from baseline in the efficacy endpoints within each treatment arm. The comparisons between Toviaz arms versus active comparator on efficacy endpoints were conducted only for exploratory purposes and are not used for efficacy evaluation.

Analysis of primary efficacy endpoint

The primary efficacy endpoint MCBC was analyzed using all subjects in the FAS. Specifically, change from baseline to Week 12 in MCBC was analyzed using an analysis of covariance (ANCOVA) including terms for treatment group, baseline MCBC and baseline weight. For each treatment, the least square (LS) mean change from baseline, standard error (SE), and 95% confidence intervals (CIs) were reported. The lower bound of the two-sided 95% CI was assessed to see if it excluded 0. Missing MCBC observations at Visit 4/Week 12 were imputed

using either last observation carried forward method (LOCF) or baseline observation carried forward method (BOCF). Per protocol, for the urodynamic data, for subjects who withdrew early prior to Week 12, and had a post-baseline urodynamic assessment at the time of withdrawal, LOCF was applied (i.e., their post-baseline urodynamic assessment conducted outside the Week 12 visit window was carried forward as the Week 12 data). For those who only had baseline urodynamic data, BOCF was used.

The applicant also conducted the following sensitivity analyses of the primary efficacy endpoint:

- ANCOVA based on PPAS
- ANCOVA based on completers of the Active Comparator Phase

***Reviewer's Note**:*

1. *FDA requested the Applicant to conduct a sensitivity analysis based on the completers of the Active Comparator Phase. The Applicant submitted the requested results on 15 February 2021.*

2. *The statistical reviewer conducted a sensitivity analysis using BOCF method to impute missing MCBC values at Visit 4/Week 12 in the FAS because in the pre-specified primary analysis of MCBC using LOCF/BOCF combined imputation method, majority of missing data at Week 12 were imputed with BOCF and LOCF was applied to only 3 subjects.*

Analysis of secondary efficacy endpoints

For the six continuous secondary efficacy endpoints, the same ANCOVA analysis for the primary endpoint was performed for each one of them. For the binary secondary efficacy endpoint "presence of IDC", cell counts and proportions for each response category are presented as a cross-tabulation with baseline and week 12 results.

All analyses of secondary efficacy endpoints were conducted using all subjects in the FAS. To be included in the analysis, all subjects need to have valid baseline data in the FAS. The same imputation rule for the primary endpoint was used for the urodynamic secondary efficacy endpoints. For the analysis of diary-based secondary efficacy endpoints, missing daily micturition data were estimated as follows:

1. If one out of three days is missing, the mean of the remaining days were used to impute the micturition data for the missing day/days.
2. The LOCF/BOCF imputation were carried out for time-intervals with missing diary data. For intervals where less than two days of diary data are available, the previously available 3-day post-baseline interval values were then be carried forward.
3. Micturition volume is collected on one day only therefore if it is missing at a visit the previous visit's data were carried forward.

3.2.4 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

The disposition of study subjects and the analysis sets are summarized for Cohort 1 in the study (Table 2). A total of 124 subjects were enrolled. These 124 subjects received treatment and 15 of them (12.1%) discontinued the treatment prematurely in the Active Comparator Phase (to Week 12). Overall, in the Active Comparator Phase, a higher proportion of subjects discontinued from the treatment in the Tovia 4 mg arm (9 subjects [21.4%]) than Tovia 8 mg arm (2 subjects [4.8%]) or the oxybutynin arm (4 subjects [10.0%]). The subject disposition information from the overall study (to Week 24) can also be found in Table 2.

Table 2 also displays an overview of efficacy populations for Cohort 1. Of the 124 patients in the Safety Set, 120 had valid baseline primary endpoint data and were included in the FAS. These 120 patients comprise the *primary analysis population* for efficacy evaluation. Of the 120 patients in the FAS, 84 were included in the PPAS (i.e., 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).

Demographics and Baseline Characteristics

The demographic and baseline characteristics for Cohort 1 are summarized in Table 3. Among all subjects in the Safety Set (N = 124), approximately half were male (55.6%); the majority were White (52.4%) or Asian (43.5%) and were Not Hispanic or Latino (95.2%). The mean age (SD) was 11.0 (2.8) years old ranging from 6 to 17 years old. The mean weight (SD) was 42.8 (14.5) kg (ranging from 25.1 to 96.0 kg). There were more children (6-11 years old) than adolescents (12-17 years old) in this study (62.1% versus 37.9%).

Furthermore, as shown in Table 3, demographic and baseline characteristics for Cohort 1 were generally well balanced between treatment arms, but there were more male subjects (n = 26) than female subjects (n = 16) in the Toviaz 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 Toviaz arms, and the proportion of Asian subjects was higher in the oxybutynin arm than in the Toviaz arms.

Table 2. Summary of Subject Disposition and Analysis Sets (Safety Set in Cohort 1)

	Toviaz 4mg n (%)	Toviaz 8mg n (%)	Oxybutynin n (%)	Total n (%)
Enrolled/Randomized/Treated	42 (100)	42 (100)	40 (100)	124 (100)
Completed study	30 (71)	36 (86)	35 (88)	101 (82)
Discontinued study	12 (29)	6 (14)	5 (13)	23 (18)
Reasons for study discontinuation				
Adverse events	3 (7)	1 (2)	0	4 (3)
Lost to follow-up	1 (2)	0	0	1 (1)
Medication error w/o associated AE	0	1 (2)	1 (3)	2 (2)
Withdraw by parent/guardian	3 (7)	1 (2)	0	4 (3)
Failure to meet randomization criteria	0	1(2)	1 (3)	2 (2)
Other	2 (5)	0	2 (5)	4 (3)
Insufficient clinical response	1 (2)	2 (5)	0	3 (2)
Protocol violation	2 (5)	0	1 (3)	3 (2)
Completed treatment (active comparator phase)	33 (78.6)	40 (95.2)	36 (90.0)	109 (87.9)
Discontinued treatment	9 (21.4)	2 (4.8)	4 (10.0)	15 (12.1)
Reasons for treatment discontinuation				
Adverse events	2 (4.8)	0	0	2 (1.6)
Lost to follow-up	1 (2.4)	0	0	1 (0.8)
Medication error w/o associated AE	0	1 (2.4)	0	1 (0.8)
Withdraw by parent/guardian	2 (4.8)	0	0	2 (1.6)
Failure to meet randomization criteria	0	1 (2.4)	1 (2.5)	2 (1.6)
Other	2(4.8)	0	2 (5.0)	4 (3.2)
Protocol violation	2(4.8)	0	1 (2.5)	3 (2.4)
Analysis set for efficacy				
FAS	41 (97.6)	41 (97.6)	38 (95.0)	120 (96.8)
PPAS	26 (61.9)	31 (73.8)	27 (67.5)	84 (67.7)

Source: Table 14.1.1.1a and Table 14.1.1.2.2a, and Table 14.1.1.2.1a in Study Report and Reviewer's Analysis
Note. The percentage is calculated using the corresponding number of Enrolled/Randomized/Treated subjects in each column as the denominator.

Table 3. Summary of Demographics and Baseline Characteristics (Safety Set in Cohort 1)

	Toviaz 4mg (N = 42)	Toviaz 8mg (N = 42)	Oxybutynin (N = 40)	Total (N = 124)
Age (Years)				
Mean (sd)	10.7 (2.7)	11.0 (2.7)	11.2 (2.9)	11.0 (2.8)
Min – Max	7 - 17	6 - 16	6 - 17	6 - 17
Age, n (%)				
>= 6 – 11	27 (64.3)	25 (59.5)	25 (62.5)	77 (62.1)
>= 12-17	15 (35.7)	17 (40.5)	15 (37.5)	47 (37.9)
Gender, n (%)				
Male	26 (61.9)	20 (47.6)	23 (57.5)	69 (55.6)
Female	16 (38.1)	22 (52.4)	17 (42.5)	55 (44.4)
Race				
White	24 (57.1)	24 (57.1)	17 (42.5)	65 (52.4)
Black	2 (4.8)	0	1 (2.5)	3 (2.4)
Asian	14 (33.3)	18 (42.9)	22 (55.0)	54 (43.5)
Other	2 (4.8)	0	0	2 (1.6)
Ethnicity				
Hispanic or Latino	3 (7.1)	2 (4.8)	1 (2.5)	6 (4.8)
Not Hispanic or Latino	39 (92.9)	40 (95.2)	39 (97.5)	118 (95.2)
Weight (kg)				
Mean (sd)	43.3 (16.2)	42.0 (12.5)	43.2 (15.0)	42.8 (14.5)
Min - Max	25.5 – 96.0	25.5 – 73.0	25.9 – 69.0	25.1 – 96.0

Source: Table 7 in Study Report and Reviewer's Analysis.
Note. The percentage is calculated using the corresponding number of Enrolled/Randomized/Treated subjects in each column as the denominator.

3.2.5 Results and Conclusions

Primary efficacy Endpoint: Maximum Cystometric Bladder Capacity (MCBC)

The analysis results for the primary efficacy endpoint are shown in Table 4. For Cohort 1, treatment with Toviaz 4 and 8 mg resulted in improvements from baseline to Week 12 in the primary efficacy endpoint MCBC, with numerically greater increase from baseline for Toviaz 8 mg than for Toviaz 4 mg. Specifically, at Week 12, patients in both Toviaz arms had an increase in MCBC compared with baseline with LS mean (SE) of 58.1 (14.8) mL and 83.4 (14.7) mL, respectively. The corresponding 95% CIs are (28.8, 87.4) and (54.2, 112.5) with lower bounds are all above 0.

Sensitivity analyses results are consistent with the primary analysis results.

Table 4. Statistical Analysis of Change from Baseline in MCBC (mL) at Week 12 (FAS in Cohort 1)

Statistic	Toviaz 4mg (N = 41)	Toviaz 8mg (N = 41)	Oxybutynin (N = 38)
Mean Baseline (SD)	195.1 (101)	173.3 (104.5)	164.1 (81.6)
Mean Week 12 (SD)	249.0 (129.3)	257 (119.5)	255.1 (108.0)
LS Mean CFB at Week 12 (SE)	58.1 (14.8)	83.4 (14.7)	87.2 (15.3)
95% CI for mean CFB	(28.8, 87.4)	(54.2, 112.5)	(56.8, 117.5)

Source: Table 9 in Study Report and Reviewer's Analysis
MCBC: maximum cystometric bladder capacity; SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline MCBC and baseline weight. Last observation carried forward/baseline observation carried forward was used for imputing missing values at Week 12. N is the number of patients who took at least one dose and provided valid MCBC values at baseline.

Secondary Efficacy Endpoints

Detrusor pressure at maximum bladder capacity (cmH_2O)

At Week 12, the LS mean change in bladder detrusor pressure at maximum bladder capacity from baseline was -2.9 cm H_2O (95% CI: -7.6, 1.9) for Toviaz 4 mg arm and -1.6 cm H_2O (95% CI: -6.3, 3.1) for Toviaz 8 mg arm.

Table 5. Statistical Analysis of Change from Baseline in Detrusor Pressure at Maximum Bladder Capacity (CMH_2O) at Week 12 (FAS in Cohort 1)

Statistic	Toviaz 4mg (N = 40)	Toviaz 8mg (N = 41)	Oxybutynin (N = 38)
Mean Baseline (SD)	26.5 (15.0)	27.2 (13.2)	23.6 (20.9)
Mean Week 12 (SD)	23.3 (14.5)	24.8 (14.6)	22.4 (21.7)
LS Mean CFB at Week 12 (SE)	-2.9 (2.4)	-1.6 (2.4)	-2.4 (2.5)
95% CI of mean CFB	(-7.6, 1.9)	(-6.3, 3.1)	(-7.3, 2.5)

Source: Table 11 in Study Report and Reviewer's Analysis
SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline endpoint and baseline weight. N is the number of patients who took at least one dose and provided valid endpoint values at baseline.

Presence of IDC

A numerically higher proportion of subjects showed improvement from baseline to Week 12 for the presence of IDC in the Toviaz 8 mg arm (18 subjects [43.9%] than Toviaz 4 mg arm (9 subjects [22.0%]).

Table 6. Presence of IDC at Baseline and Week 12 (FAS in Cohort 1)

		Week 12					
		Toviaz 4mg (N = 41)		Toviaz 8mg (N = 41)		Oxybutynin (N = 38)	
	Presence of IDC?	Yes	No	Yes	No	Yes	No
Baseline	Yes	18 (43.9)	9 (22.0)	18 (43.9)	18 (43.9)	18 (47.4)	14 (36.8)
	No	2 (4.9)	12 (29.3)	1 (2.4)	4 (9.8)	0	6 (15.8)

Source: Table 13 in Study Report and Reviewer's Analysis

Bladder Volume at First IDC

At Week 12, the LS mean change in bladder volume at first IDC from baseline was 30.5 mL (95% CI 2.4, 58.6) for Toviaz 4 mg arm and 26.1 mL (95% CI: 2.2, 49.9) for Toviaz 8 mg arm.

Table 7. Statistical Analysis of Change from Baseline in Bladder Volume at First IDC at Week 12 (FAS in Cohort 1)

Statistic	Toviaz 4mg (N = 26)	Toviaz 8mg (N = 36)	Oxybutynin (N = 32)
Mean Baseline (SD)	88.6 (73.8)	88.5 (76.2)	76.8 (51.2)
Mean Week 12 (SD)	118.0 (101.2)	113.8 (84.3)	119.9 (89.0)
LS Mean CFB at Week 12 (SE)	30.5 (14.1)	26.1 (12.0)	41.3 (12.8)
95% CI of mean CFB	(2.4, 58.6)	(2.2, 49.9)	(15.9, 66.7)

Source: Table 15 in Study Report and Reviewer's Analysis
SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline endpoint and baseline weight. N is the number of patients who took at least one dose and provided valid endpoint values at baseline.

Bladder Compliance

At Week 12, the LS mean change in bladder compliance from baseline was 6.4 mL/cm H_2O (95% CI: -0.5, 13.3) for Toviaz 4 mg arm and 5.4 mL/cm H_2O (95% CI: -1.5, 12.3) for Toviaz 8 mg arm.

Table 8. Statistical Analysis of Change from Baseline in Bladder Compliance (ML/CMH_2O) at Week 12 (FAS in Cohort 1)

Statistic	Toviaz 4mg (N = 40)	Toviaz 8mg (N = 40)	Oxybutynin (N = 38)
Mean Baseline (SD)	13.8 (19.0)	10.1 (11.2)	14.2 (17.0)
Mean Week 12 (SD)	19.2 (20.6)	17.7 (18.8)	24.2 (25.9)
LS Mean CFB at Week 12 (SE)	6.4 (3.5)	5.4 (3.5)	11.4 (3.6)
95% CI of mean CFB	(-0.5, 13.3)	(-1.5, 12.3)	(4.3, 18.4)

Source: Table 17 in Study Report and Reviewer's Analysis
SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline endpoint and baseline weight. N is the number of patients who took at least one dose and provided valid endpoint values at baseline.

Mean Volume Voided per Catheterization

At Week 12, the LS mean change in mean volume voided per catheterization from baseline was 29.5 mL (95% CI: -1.4, 60.3) for Toviaz 4 mg arm and 47.2 mL (95% CI: 14.7, 79.6) for Toviaz 8 mg arm.

Table 9. Statistical Analysis of Change from Baseline in Bladder Compliance (mL) at Week 12 (FAS in Cohort 1)

Statistic	Toviaz 4mg (N = 36)	Toviaz 8mg (N = 32)	Oxybutynin (N = 28)
Mean Baseline (SD)	147.8 (78.7)	118.2 (66.6)	118.2 (65.2)
Mean Week 12 (SD)	179.9 (156.4)	163.7 (99.9)	162.6 (88.7)
LS Mean CFB at Week 12 (SE)	29.5 (15.5)	47.2 (16.3)	45.9 (17.4)
95% CI of mean CFB	(-1.4, 60.3)	(14.7, 79.6)	(11.2, 80.6)

Source: Table 30 in Study Report and Reviewer's Analysis
SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline endpoint and baseline weight. N is the number of patients who took at least one dose and provided valid endpoint values at baseline.

Mean Number of Incontinence Episodes per 24 Hours

At Week 12, the LS mean change in mean number of incontinence episodes per 24 hours from baseline was -0.5 (95% CI: -0.9, -0.0) for Toviaz 4 mg arm and -0.9 (95% CI: -1.4, -0.4) for Toviaz 8 mg arm.

Table 10. Statistical Analysis of Change from Baseline in Mean Number of Incontinence Episodes Per 24 hours at Week 12 (FAS in Cohort 1)

Statistic	Toviaz 4mg (N = 33)	Toviaz 8mg (N = 33)	Oxybutynin (N = 35)
Mean Baseline (SD)	2.8 (1.8)	2.7 (1.5)	3.1 (2.4)
Mean Week 12 (SD)	2.4 (1.6)	1.9 (1.5)	2.0 (1.5)
LS Mean CFB at Week 12 (SE)	-0.5 (0.2)	-0.9 (0.2)	-1.0 (0.2)
95% CI of mean CFB	(-0.9, -0.0)	(-1.4, -0.4)	(-1.5, -0.6)

Source: Table 25 in Study Report and Reviewer's Analysis
SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline endpoint and baseline weight. N is the number of patients who took at least one dose and provided valid endpoint values at baseline. Only patients with > 0 incontinence episodes at baseline are included.

Maximum Catheterized Urine Volume per 24 Hours

At Week 12, the LS mean change in maximum catheterized urine volume per 24 hours from baseline was 31.6 mL (95% CI: -9.3, 72.6) for Toviaz 4 mg arm and 51.0 mL (95% CI: 8.1, 93.8) for Toviaz 8 mg arm.

Table 11. Statistical Analysis of Change from Baseline in Maximum Catheterized Urine Volume Per 24 hours (mL) at Week 12 (FAS in Cohort 1)

Statistic	Toviaz 4mg (N = 36)	Toviaz 8mg (N = 32)	Oxybutynin (N = 28)
Mean Baseline (SD)	222.5 (102.1)	164.7 (90.3)	169.6 (91.6)
Mean Week 12 (SD)	245.6 (164.5)	221.3 (117.8)	227.9 (125.9)
LS Mean CFB at Week 12 (SE)	31.6 (20.6)	51.0 (21.6)	53.8 (22.9)
95% CI of mean CFB	(-9.3, 72.6)	(8.1, 93.8)	(8.2, 99.3)

Source: Table 14.2.15.1.1a in Information Request response submitted on 8 April 2021 and Reviewer's Analysis
SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline endpoint and baseline weight. N is the number of patients who took at least one dose and provided valid endpoint values at baseline.

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Efficacy of Toviaz was also explored by subgroups defined by gender (female, male), age (≥ 6-11 years old, ≥12-17 years old), race (White, Asian, Black, Other), and region (North America, Europe, Asia) based on data in the FAS (see Appendix). The same ANCOVA model with missing data imputed was applied to these subgroup analyses.

As shown in Tables 14 - 17 in Appendix, in all subgroups except for the European subjects receiving Toviaz 4 mg, there was an increase in the MCBC from baseline to Week 12 for both Toviaz 4 mg and 8 mg. For the subgroup of European subjects receiving Toviaz 4 mg, the estimated change from baseline was 47.5 mL with 95% CI covering zero (95% CI: -4.9, 99.8). However, due to the limited number of European subjects, no definitive conclusion can be drawn. Note that for the racial subgroups of "Black" and "Other", the model-based change from baseline in MCBC was not estimable due to the small sample size (Black: n = 2 for Toviaz 4 mg and n = 1 for Toviaz 8 mg; Other: n = 1 for Toviaz 4 mg and n = 0 for Toviaz 8 mg).

Reviewer's Note:

1. *The ANCOVA subgroup analyses were conducted by the statistical reviewer. The pre-specified subgroup analyses were descriptive summary of change from baseline in the primary efficacy endpoint within subgroups based on observed data in the FAS.*

2. *The FAS for Cohort 1 includes 3 South African subjects. Given low numbers of subjects in South Africa, the Applicant pooled South Africa with Asian countries for subgroup analysis by region. This pooling strategy was agreed upon with FDA at the September 10, 2020 pre-NDA meeting.*

4.2 Other Special/Subgroup Populations

The Applicant originally proposed a dosing regimen of Toviaz 4 mg for subjects with a body weight ≥ (b) (4) kg to ≤ 35 kg and Toviaz 8 mg for subjects with a body weight > 35 kg based on data from both cohorts. To support their dosing recommendation, the Applicant provided post-hoc descriptive summaries of the primary efficacy endpoint for two weight subgroups (>25 to ≤ 35 kg and > 35 kg) based on subjects in Cohort 1 who had observed MCBC data at Week 12 (see Table 12). As shown in Table 12, for subjects > 25 kg to ≤ 35 kg, the observed mean changes from baseline in MCBC at Week 12 are similar between Toviaz 4 mg and 8 mg arms (47.2 versus 53.2 mL); for subjects >35 kg, Toviaz 8 mg has numerically greater increase from baseline compared to 4 mg (120.0 versus 76.0 mL). (b) (4)

Table 12. Descriptive Summary of Change from Baseline in MCBC (mL) at Week 12 - Weight Subgroup (FAS in Cohort 1)

Statistics	Weight > 25 kg to ≤ 35 kg		Weight > 35 kg	
	Toviaz 4 mg	Toviaz 8 mg	Toviaz 4 mg	Toviaz 8 mg
N	13	13	21	27
Mean (SD)	47.2 (43.6)	53.2 (64.7)	76.0 (103.3)	102.0 (105.3)
Median	42.0	40.0	84.0	113.0
Min	-11.0	-32.0	-68.0	-69.0
Max	120.0	171.0	410.0	376.0

Source. Table 12 in Summary of Clinical Efficacy and Reviewer's Analysis
MCBC: maximum cystometric bladder capacity; BIC: beads-in-capsule; SD: standard deviation; Min: minimum; Max: maximum
N is the number of patients who took at least one dose and provided valid MCBC data at both baseline and Week 12.

In addition, the statistical reviewer analyzed the primary efficacy endpoint using the same ANCOVA model with missing data imputed for the above weight subgroups and the results are presented in Table 13.

The efficacy analyses demonstrate that both dosing groups are effective in the two weight subgroups with the lower bound of the 95% CI for the estimated LS mean in MCBC change at Week 12 greater than zero. Toviaz 8 mg had numerically greater increase in MCBC from baseline compared to Toviaz 4 mg for both weight subgroups. Due to the limitations of the study design, there is no adequate power to compare the two doses within each weight subgroup using the formal statistical testing approach.

Table 13. Statistical Analysis of Change from Baseline in MCBC (mL) at Week 12- Weight Subgroup (FAS in Cohort 1)

Statistic	Weight > 25 kg to ≤ 35 kg		Weight > 35 kg	
	Toviaz 4 mg	Toviaz 8 mg	Toviaz 4 mg	Toviaz 8 mg
N	16	13	25	28
Mean baseline (SD)	150.6 (72.1)	155.2 (98.3)	223.6 (107.2)	181.6 (107.9)
Mean week 12 (SD)	189.0 (92.5)	208.4 (101.3)	287.5 (136.4)	280.0 (122.1)
LS Mean CFB at Week 12 (95% CI)	39.4 (2.4, 76.5)	57.8 (16.6, 98.9)	73.1 (32.0, 114.3)	91.8 (53.1, 130.5)

Source: Table 14.2.2.5.3a and Table 14.2.2.5.4a in Information Request response submitted on 8 April 2021 and Reviewer's Analysis
MCBC: maximum cystometric bladder capacity; SD: standard deviation; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline MCBC and baseline weight. Last observation carried forward/baseline observation carried forward was used for imputing missing values at Week 12. N is the number of patients who took at least one dose and provided valid MCBC values at baseline.

From a statistical perspective, considering both the descriptive statistics for the observed data and the model-estimated mean change from baseline for the primary efficacy endpoint, starting all subjects on the 4 mg and increasing the dose to 8 mg is reasonable in both weight subgroups. For the subjects weighing >25 kg - ≤ 35 kg, this dose up-titration can be made if needed given subjects have no safety or tolerability issues.

4.3 Statistical Issues and Collective Evidence

The Applicant submitted an open-label, randomized, 3-arm, phase 3 study to evaluate the efficacy and safety of Toviaz 4 mg and 8 mg tablet in pediatric patients weighing > 25 kg and to partially fulfill the written request. Even though the study had a control group, it does not serve as a comparator for efficacy evaluation. The evaluation of the treatment effect on efficacy is based on the change from baseline within each treatment arm.

The primary and selected secondary efficacy endpoints based on the urodynamic assessments and patient diaries demonstrated improvement at Week 12 compared to baseline in general.

4.4 Conclusions and Recommendations

The purpose of this review is to evaluate the efficacy data in support of Toviaz 4 mg and 8 mg tablet for the treatment of NDO in pediatric patients. Based on reviewer's analyses, the submitted study demonstrated clinical benefit for this indication in pediatric patients at least 6 years old and weighing greater than 25 kg.

APPENDIX

Table 14. Statistical Subgroup Analysis of Change from Baseline in MCBC (mL) at Week 12 by Gender (FAS in Cohort 1)

	Statistic	Toviaz 4mg	Toviaz 8mg
Female	N	16	21
	Mean Baseline (SD)	179.9 (94.5)	167.5 (83.5)
	Mean Week 12 (SD)	237.7 (103.6)	258.7 (118.4)
	LS Mean CFB at Week 12 (SE)	58.6 (20.0)	89.2 (17.4)
	95% CI for mean CFB	(18.3, 98.8)	(54.2, 124.3)
Male	N	25	20
	Mean Baseline (SD)	204.8 (105.3)	179.3 (124.7)
	Mean Week 12 (SD)	256.3 (145.0)	255.8 (123.6)
	LS Mean CFB at Week 12 (SE)	56.6 (21.6)	76.0 (24.2)
	95% CI for mean CFB	(13.4, 99.9)	(27.6, 124.5)

Source: Reviewer's Analysis
MCBC: maximum cystometric bladder capacity; SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline MCBC and baseline weight. Last observation carried forward/baseline observation carried forward was used for imputing missing values at Week 12. N is the number of patients who took at least one dose and provided valid MCBC values at baseline.

Table 15. Statistical Subgroup Analysis of Change from Baseline in MCBC (mL) at Week 12 by Race (FAS in Cohort 1)

	Statistic	Toviaz 4mg	Toviaz 8mg
Asian	N	14	18
	Mean Baseline (SD)	199.1 (84.2)	195.6 (101.1)
	Mean Week 12 (SD)	259.6 (104.4)	286.3 (109.4)
	LS Mean CFB at Week 12 (SE)	62.5 (22.8)	90.9 (20.1)
	95% CI for mean CFB	(16.7, 108.4)	(50.5, 131.3)
White	N	23	23
	Mean Baseline (SD)	200.4 (114.3)	155.8 (105.9)
	Mean Week 12 (SD)	245.9 (152.8)	234.6 (124.4)
	LS Mean CFB at Week 12 (SE)	54.0 (22.4)	77.3 (22.1)
	95% CI for mean CFB	(9.04, 98.9)	(33.0, 121.5)
Black	N	2	1
	Mean Baseline (SD)	125.0 (35.4)	144.0 (-)
	Mean Week 12 (SD)	185.0 (49.5)	123.0 (-)
	LS Mean CFB at Week 12 (SE)	-	-
	95% CI for mean CFB	-	-
Other	N	2	0
	Mean Baseline (SD)	176.0 (116.0)	-
	Mean Week 12 (SD)	275.0 (7.1)	-
	LS Mean CFB at Week 12 (SE)	-	-
	95% CI for mean CFB	-	-

Source: Reviewer's Analysis
MCBC: maximum cystometric bladder capacity; SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline MCBC and baseline weight. Last observation carried forward/baseline observation carried forward was used for imputing missing values at Week 12. N is the number of patients who took at least one dose and provided valid MCBC values at baseline.

Table 16. Statistical Subgroup Analysis of Change from Baseline in MCBC (mL) at Week 12 by Age (FAS in Cohort 1)

	Statistic	Toviaz 4mg	Toviaz 8mg
6-11 years old	N	27	24
	Mean Baseline (SD)	177.5 (91.2)	159.0 (111.0)
	Mean Week 12 (SD)	222.0 (109.6)	248.8 (113.6)
	LS Mean CFB at Week 12 (SE)	53.2 (15.5)	87.4 (16.3)
	95% CI for mean CFB	(22.2, 84.2)	(54.8, 119.9)
12-17 years old	N	14	17
	Mean Baseline (SD)	229.1 (112.7)	193.4 (94.0)
	Mean Week 12 (SD)	301.1 (151.7)	269.4 (129.9)
	LS Mean CFB at Week 12 (SE)	80.2 (31.2)	69.2 (28.3)
	95% CI for mean CFB	(17.3, 143.2)	(12.0, 126.4)

Source: Reviewer's Analysis
MCBC: maximum cystometric bladder capacity; SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline MCBC and baseline weight. Last observation carried forward/baseline observation carried forward was used for imputing missing values at Week 12. N is the number of patients who took at least one dose and provided valid MCBC values at baseline.

Table 17. Statistical Subgroup Analysis of Change from Baseline in MCBC (mL) at Week 12 by Region (FAS in Cohort 1)

	Statistic	Toviaz 4mg	Toviaz 8mg
North America	N	5	5
	Mean Baseline (SD)	250.2 (109.9)	154.8 (113.4)
	Mean Week 12 (SD)	315.0 (131.1)	239.6 (145.8)
	LS Mean CFB at Week 12 (SE)	96.5 (39.0)	89.1 (28.1)
	95% CI for mean CFB	(6.5, 186.5)	(24.3, 153.9)
Asia	N	18	19
	Mean Baseline (SD)	178.6 (84.5)	192.2 (97.1)
	Mean Week 12 (SD)	241.5 (104.2)	275.7 (111.3)
	LS Mean CFB at Week 12 (SE)	62.9 (21.2)	85.4 (20.6)
	95% CI for mean CFB	(20.4, 105.3)	(44.1, 126.8)
Europe	N	18	17
	Mean Baseline (SD)	196.3 (112.8)	157.5 (112.5)
	Mean Week 12 (SD)	238.3 (151.6)	241.9 (125.3)
	LS Mean CFB at Week 12 (SE)	47.5 (25.9)	83.8 (26.5)
	95% CI for mean CFB	(-4.9, 99.8)	(30.2, 137.4)

Source: Reviewer's Analysis
MCBC: maximum cystometric bladder capacity; SD: standard deviation; SE: standard error; CI: confidence interval; CFB: change from baseline; LS: least square
Note. LS mean estimate of CFB and its corresponding 95% CIs are based on ANCOVA model with terms for treatment group, baseline MCBC and baseline weight. Last observation carried forward/baseline observation carried forward was used for imputing missing values at Week 12. N is the number of patients who took at least one dose and provided valid MCBC values at baseline.

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