NDA/BLA Multidisciplinary Review and Evaluation

Application Type	SE-8, Labeling Supplement with Clinical Data
Application Number(s)	sBLA 103000 / S-5325
Priority or Standard	Standard
Submit Date(s)	October 14, 2022
Received Date(s)	October 14, 2022
PDUFA Goal Date	August 14, 2023
Division/Office	Division of Urology, Obstetrics, and Gynecology/Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Review Completion Date	July 21, 2023
Established/Proper Name	OnabotulinumtoxinA
Trade Name	BOTOX
Pharmacologic Class	Acetylcholine release inhibitor
Code name	
Applicant	Allergan, Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	N/A
Applicant Proposed Indication(s)/Population(s)	N/A
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	N/A
Recommendation on Regulatory Action	Approval of Labeling Supplement
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	N/A

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Abbreviations: COA, clinical outcome assessment; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OMP, Office of Medical Policy; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

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Glossary

ADME	absorption, distribution, metabolism, excretion
ADSL	Subject-Level Analysis Dataset
AE	adverse event
BAB	binding antibodies
BLA	biologics license application
CDTL	Cross-Discipline Team Leader
CIC	clean intermittent catheterization
COA	Clinical Outcome Assessment
DHOT	Division of Hematology Oncology Toxicology
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DUOG	Division of Urology, Obstetrics, and Gynecology
eCTD	electronic common technical document
FDA	Food and Drug Administration
IND	Investigational New Drug
LOCF	last observation carried forward
LUT	lower urinary tract
MedDRA	Medical Dictionary for Regulatory Activities
MG	medication guide
MMRM	mixed-effect model repeated measures
NDA	new drug application
NDO	neurogenic detrusor overactivity
OAB	overactive bladder
OCP	Office of Clinical Pharmacology
PDSOT	potential distant spread of toxin
PI	prescribing information
PinQ	Pediatric Incontinence Questionnaire
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PVR	postvoid residual
SAE	serious adverse event
sBLA	supplemental biologics license agreement
TBS	treatment benefit scale
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse events
UTI	urinary tract infection

1 Executive Summary

1.1. Product Introduction

BOTOX (onabotulinumtoxinA) is sterile, vacuum-dried purified botulinum toxin type A. Botulinum toxin is a neuromuscular blocking agent that prevents muscular contraction by inhibiting release of acetylcholine at the neuromuscular junction. BOTOX was initially approved in the U.S. in 1989 and was subsequently approved for multiple indications. BOTOX is currently approved for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication. The approval for the adult OAB indication included a requirement for pediatric assessment under the Pediatric Research Equity Act (PREA, 21 USC 355c).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Sponsor submitted the sBLA under Section 351(a) of the PHS Act as a SE-8 Labeling Supplement to the existing marketing application for BOTOX (BLA 103000) for the addition of pediatric OAB clinical data to Section 8.4 of the current approved labeling for BOTOX.

To address the PREA requirement accompanying the approval of BOTOX for adult OAB, BOTOX was studied in a clinical trial including 55 children ages 12 years to 17 years with OAB. Study 191622-137 is a Phase 3, multicenter, randomized, double-blind, parallel group study in patients with OAB 12 to 17 years of age who had not been adequately managed with anticholinergic therapy. Subjects were randomized into one of 3 treatment groups in a 1:1:1 ratio receiving 25 U (units), 50 U, or 100 U of BOTOX, not to exceed 6 U per kilogram. Doses were administered via intradetrusor injection on day 1, with an option of retreatment at least 12 weeks after the previous treatment.

This study assessed drug effect on clinical outcomes recorded in a patient urinary diary, including daytime urinary incontinence episodes (primary endpoint) and several secondary outcomes. The study was ended prior to full enrollment of the planned sample size of 108 subjects, due to challenges enrolling the targeted population of adolescents. This was related to the fact that the peak incidence of OAB in children is age 5 to 7 years, and thereafter starts to decrease with age. The primary efficacy analysis from Study 191622-137 did not demonstrate efficacy of either 50 U BOTOX or 100 U BOTOX compared to 25 U BOTOX. There was no statistically significant difference in the mean change from baseline in the daily average frequency of daytime urinary incontinence episodes (primary efficacy endpoint) at Week 12 post-treatment 1.

The safety profile of BOTOX for the treatment of OAB in children 12 to 17 years of age was comparable to the known safety profile of BOTOX for the treatment of OAB in adults. Adverse

reactions including urinary tract infection (UTI), urinary retention, and residual urine volume were similar to the adult OAB program. Specific to BOTOX as a product, there are labelled safety concerns for potential distant spread of toxin (PDSOT). Therefore, the benefit-risk balance for the 50 U BOTOX or 100 U BOTOX doses compared to 25 U BOTOX dose (the comparator group) was not favorable due to the lack of demonstrated efficacy and the known safety profile. We conclude that neither BOTOX 50 U nor BOTOX 100 U is an effective second line treatment in children 12 to 17 years of age with OAB who have not been adequately managed with anticholinergic therapy. We recommend approval of SE-8, (a Labeling Supplement with clinical data) for proposed changes to Section 8.4 of the Prescribing Information (PI), for informational purposes regarding the results of Study 191622-137.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pediatric idiopathic overactive bladder (OAB) is a functional condition of the lower urinary tract (LUT), with no discernable underlying neurologic or anatomic abnormality. OAB describes a daytime condition in which children experience urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other pathology (Austin et al. 2014). The underlying pathophysiology of bladder and bowel dysfunction (BBD) is not fully understood; however, BBD often co-exists with OAB and is considered an umbrella term that is subcategorized into LUT dysfunction and bowel dysfunction.[1] One theory is that rectal distention causes mechanical pressure on the bladder wall, leading to OAB and poor bladder emptying. Another theory proposes that since there is common neural input of the urethral and rectal sphincters, chronic contraction of the anal sphincter due to rectal stool impaction leads to pelvic floor contraction, secondary detrusor sphincter dyssynergia, and a vicious cycle leading to bladder overactivity, urinary incontinence, recurrent urinary tract infection (UTI), and vesicoureteral reflux. A third hypothesis is that this pathophysiology is centrally mediated (Austin and Vricella 2015).

Pediatric LUT disorders are common and account for up to 40% of visits to pediatric urology clinics. 22% of school age children reported LUT dysfunction symptoms, most commonly holding urine and urgency. The peak incidence is age 5 to 7 years of age, and thereafter starts to decrease with age (Austin and Abhishek 2021).[2] Children with functional disorders of the urinary tract have an increased risk of urinary tract infection, vesicoureteral reflux, and renal impairment, and experience a negative effect on quality of life. 20 to 40% of children with daytime urinary incontinence have concomitant behavioral disorders (Austin and Vricella 2015).

Evaluation involves a history including experience with toilet training, and bladder and bowel symptoms. Focused physical examination includes evaluation of the abdomen, lower back, neurological and genitourinary examinations. Testing may include urinalysis, urine culture, abdominal X-Ray, or ultrasound to assess the stool burden, and an ultrasound of the kidneys and bladder pre and post void. Uroflowmetry and

[1] ibid

[2] ibid

electromyography may be performed. More rarely, formal urodynamics with an indwelling urethral catheter may be considered but is more invasive.

The management goal is to improve LUT symptoms, reduce recurrent UTI if present, and prevent kidney damage. Conservative management starts with behavioral modifications of voiding, treatment of constipation, education, and tracking of symptoms and habits. If symptoms persist, biofeedback using real-time uroflowmetry and patch electromyography data may be used to treat voiding dysfunction and prevent detrusor sphincter dyscoordination.[3] Anticholinergics such as oxybutynin may be used off label for symptoms of OAB in children but cause unwanted effects such as constipation, increased bladder post void residual, dry mouth, and reduced sweating. Alpha-adrenergic receptor antagonists such as doxazosin have also been used for the treatment of LUT dysfunction in children to decrease bladder outlet resistance but may be associated with adverse events such as hypotension or dizziness. Intravesical botulinum toxin injection and neuromodulation have been studied as investigational treatment modalities in children (Austin and Vricella 2015).

BOTOX (onabotulinumtoxinA) is sterile, vacuum-dried purified botulinum toxin type A. Botulinum toxin is a neuromuscular blocking agent that prevents muscular contraction by inhibiting release of acetylcholine at the neuromuscular junction. BOTOX was initially approved in the U.S. in 1989 and is currently approved for multiple indications. BOTOX is currently approved for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication. The approval for the adult OAB indication included a requirement for pediatric assessment, under the Pediatric Research Equity Act (PREA, 21 USC 355c).

To address the PREA requirement accompanying the approval of BOTOX for adult OAB, BOTOX was studied in one clinical trial in 55 children ages 12 to 17 years with OAB. Study 191622-137 was a Phase 3, multicenter, randomized, double-blind, parallel group study in patients with OAB 12 to 17 years of age. Subjects were randomized into one of 3 treatment groups in a 1:1:1 ratio receiving either 25 U, 50 U, or 100 U of BOTOX not to exceed 6 U per kilogram. Doses were administered via intra-detrusor injection on Day 1, with optional retreatment 12 weeks after the previous treatment. This study assessed drug effect on clinical outcomes recorded in a patient urinary diary, including daytime urinary incontinence episodes (primary endpoint) and several secondary outcomes.

[3] ibid

The study medication was administered via cystoscopy as 20 intradetrusor injections of 0.5 mL each, sparing the trigone.[4] According to the study report, after treatment on Day 1, subjects were seen at clinic visits at Weeks 2, 6, and 12 post-treatment. Patients could request retreatment starting from Week 12 after the previous study treatment. At retreatment, the investigator could either keep the same dose or request a dose increase if the previous dose was well tolerated but there was an insufficient response. Subjects completed the study once 96 weeks from entry into the study at Day 1, and at least 12 weeks follow-up since their last treatment had occurred.[5]

The study was ended prior to full enrollment of the planned sample size of 108 subjects, due to enrollment challenges. The primary efficacy analysis did not demonstrate efficacy of either 50 U BOTOX or 100 U BOTOX compared to 25 U BOTOX in terms of the mean change from study baseline in daily average frequency of daytime urinary incontinence episodes at Week 12 post-treatment 1. The safety profile of BOTOX for the treatment of OAB in children 12 to 17 years of age was comparable to the known safety profile of BOTOX for the treatment of OAB in adults. Adverse reactions including UTI, urinary retention, and increased residual urine volume were similar to the adult OAB program. Specific to BOTOX as a product, known labelled safety concerns remain for potential distant spread of toxin (PDSOT).

The benefit-risk balance for the 50 U BOTOX or 100 U BOTOX doses compared to 25 U BOTOX dose (the comparator group) was not favorable due to the lack of demonstrated efficacy and the known safety profile. We conclude that neither BOTOX 50 U nor BOTOX 100 U is an effective second line treatment in children ages 12 to 17 years of age who have not been adequately managed with anticholinergic therapy. We recommend approval of SE-8, (a Labeling Supplement with clinical data) for proposed changes to Section 8.4 of the PI for informational purposes regarding the results of Study 191622-137.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Idiopathic pediatric OAB is a daytime condition in which children experience urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection or	Pediatric idiopathic OAB is a common condition that may cause urinary frequency, urinary incontinence, and decreased quality of

[4] 191622-137 Study Report/Synopsis, page 2/6.

[5] ibid

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	other pathology. • OAB is a functional condition of the LUT, with no discernable underlying neurologic or anatomic abnormality. • The underlying pathophysiology of BBD is not understood. • Pediatric LUT disorders are common, may be associated with other comorbidities, and usually improve over time. • Management goals include improving LUT symptoms, reducing recurrent UTI if present, and preventing kidney damage.	life. However, in most patients, symptoms resolve over time.
Current Treatment Options	• Conservative management with behavioral modifications, treatment of constipation, education, and tracking of symptoms and habits. • Biofeedback using real-time uroflowmetry and patch electromyography data may be used to treat voiding dysfunction and prevent detrusor sphincter dyscoordination. • Anticholinergics such as oxybutynin are used off label for symptoms of OAB in children but may cause unwanted effects such as constipation, increased bladder post void residual, dry mouth, and reduced sweating. • Alpha-adrenergic receptor antagonists such as doxazosin have also been used for the treatment of LUT dysfunction in children, to decrease bladder outlet resistance but may be associated with adverse events such as hypotension or dizziness. • Neuromodulation is an investigational treatment.	Intravesical BOTOX injection is an invasive procedure requiring general anesthesia in children with idiopathic overactive bladder. Noninvasive treatment modalities are available to treat children with this condition.
Benefit	• The primary efficacy analysis did not demonstrate efficacy of either 50 U BOTOX or 100 U BOTOX compared to 25 U BOTOX in terms of the mean change from study baseline in daily average frequency of daytime urinary	The comparisons of 50 U and 100 U doses to 25 U dose were not statistically significant and the efficacy endpoint was not met.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	incontinence episodes at Week 12 post-treatment 1.	
Risk and Risk Management	• BOTOX requires a surgical procedure (cystoscopy) for which patients receive anesthesia and preprocedural antibiotics. BOTOX is then administered via cystoscopy, with 20 injections of 0.5 mL each into the detrusor muscle, avoiding the trigone. • The safety profile of BOTOX for the treatment of OAB in children 12 to 17 years of age was comparable to the safety profile of BOTOX for the treatment of OAB in adults. • Adverse reactions including UTI, urinary retention, and residual urine volume were similar to the adult OAB program. • The most reported treatment-emergent adverse events (TEAEs) were nasopharyngitis, dysuria, UTI, and abdominal pain. • There was no evidence of distant spread of toxin (DSOT) in the clinical studies; however, PDSOT remains a boxed warning for the product. • With the limited number of subjects who tested positive for binding antibodies (BAB), no conclusion can be made regarding the impact of immunogenicity on safety.	One of the expected adverse events with intravesical BOTOX injection is urinary retention that may require postoperative clean intermittent catheterization (CIC). Clean intermittent catheterization via the urethra may be difficult for children with sensitive mucosa. The risk of urinary retention requiring CIC in children with normal sensation, the risks of general anesthesia, and urinary tract infection with BOTOX injection procedures, outweigh any potential benefit in this condition. A description of Study 191622-137 is added to Section 8.4 of the BOTOX label.

1.4. Patient Experience Data

Table 1. Patient Experience Data Relevant to This Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		

☐	**Patient experience data that were not submitted in the application, but were considered in this review:**		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	**Patient experience data was not submitted as part of this application.**		

2 Therapeutic Context

2.1. Analysis of Condition

The normal micturition cycle involves low-pressure filling of the bladder during the urine storage phase and coordination of detrusor contraction with urinary sphincter relaxation during voiding. Pediatric OAB is defined by the International Children's Continence Society as a daytime condition in which children experience urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other pathology (Austin et al. 2014). OAB symptoms are caused by an abnormal bladder contraction during the filling phase of the bladder.[6] Pediatric OAB is a functional condition of the lower urinary tract with no underlying neurologic or anatomic abnormality. The etiology of pediatric OAB is not fully understood. However, pediatric lower urinary tract dysfunction is known to be associated with bladder and bowel dysfunction (Austin et al. 2014).

Pediatric lower urinary tract (LUT) disorders are common and account for up to 40% of visits to pediatric urology clinics (Austin and Abhishek 2021). 22% of school age children reported LUT dysfunction symptoms, most commonly holding urine and urgency. The peak incidence is age 5 to 7 years of age, and thereafter starts to decrease with age (Austin and Abhishek 2021).[7] Children with functional disorders of the urinary tract have an increased risk of urinary tract infection, vesicoureteral reflux, and renal impairment, and experience a negative effect on quality of life (Austin and Vricella 2015). LUT dysfunction is associated with VUR, and treatment of LUT dysfunction has been shown to improve the VUR resolution rate (Austin and Vricella 2015).

Children with OAB are usually evaluated with an ultrasound of the bladder; in addition, uroflowmetry and urodynamics may be performed. The management goals include improvement of LUT symptoms and prevention of UTI and kidney damage. These goals are primarily achieved with education, behavioral modifications, and treatment of constipation.

2.2. Analysis of Current Treatment Options

Management of pediatric OAB starts with behavioral modifications of voiding, treatment of constipation, education, and tracking of symptoms and habits. If symptoms persist, biofeedback, using real-time uroflowmetry and patch electromyography data, may be used to treat voiding dysfunction. This modality helps to prevent detrusor sphincter dyscoordination (Austin and Vricella 2015). Anticholinergics such as oxybutynin are used off-label for symptoms

[6] Nepple KG, et al: Etiology and clinical features of bladder dysfunction in children. UpToDate, 2023.

[7] ibid

of OAB in children but may cause side effects such as constipation, increased bladder post void residual, dry mouth, and reduced sweating. Alpha-adrenergic receptor antagonists such as doxazosin have also been used for the treatment of LUT dysfunction in children, to decrease bladder outlet resistance, but may be associated with side effects such as hypotension or dizziness. Intravesical botulinum toxin injection and neuromodulation have been studied as investigational treatment modalities in children. Table 2 summarizes of the treatment armamentarium for pediatric OAB that is used off-label in clinical practice (Chang et al. 2017; Tekgul et al. 2020).[8]

Table 2. Summary of Treatment Armamentarium Relevant to the Proposed Indication

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Approved products:				
None				
Unapproved Products used off-label:				
Oral	Antimuscarinics			
	oxybutynin	2.5 mg or 5 mg tablet		071655 074625 075079 208165 209025 209335 209823 210125 210611 211062 211682 212798 213550
		5 mg/5 ml syrup (0.3-0.6 mg/kg/day in 3 doses)		074520 075137
	Ditropan XL/oxybutynin chloride	5 mg or 10 mg, extended-release tablet	020897	
	Ditropan XL/oxybutynin chloride	5 mg, 10 mg, or 15 mg extended-release tablet		078503 202332 204010 206121 207138 210717 211655 214415
	Detrol/tolterodine	1 mg or 2 mg tablet	020771	
	tolterodine tartrate	1 mg or 2 mg tablet (0.5-2 mg/day)		077006 203409 204397

[8] ibid

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
				204721 205399 210775
	Vesicare/solifenacin	5 mg or 10 mg tablets (1.25-10 mg)	021518	
	solifenacin succinate	5 mg or 10 mg tablets		091464 202551 205575 206817 209239 209333 209839 210224 210281 210582 210688 211423 211657 211701 212214 215761
	Trospium chloride	20 mg tablet (10-25mg total daily dosage, split into two doses)		091513 091573 091575 091688 204945 215781
Transdermal	Antimuscarinics			
	Oxytrol/oxybutynin	3.9mg/24HR film, extended release	021351	

Source: Reviewer designed table using:
Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed February 17, 2023.
Drugs@FDA website accessed February 17, 2023.
Daily Med website accessed May 2, 2023.
DAARTS
Abbreviations: ANDA, abbreviated new drug application; NDA, new drug application

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BOTOX (onabotulinumtoxinA) was first approved in the U.S. in 1989 and is currently approved for the following indications:

- Treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication

- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury, multiple sclerosis] in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer)
- Treatment of upper and lower limb spasticity in patients 2 years of age and older
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Treatment of blepharospasm associated with dystonia in patients 12 years of age and older
- Treatment of strabismus in patients 12 years of age and older

BLA 103000/S-5251 BOTOX was approved on 1/18/2013 for the treatment of overactive bladder in adults who have had an inadequate response to or are intolerant of an anticholinergic medication, with a PREA postmarketing requirement (#2724-3). Allergan was required to conduct a pediatric study using dosages calibrated for pediatric use. Results of the PREA postmarketing requirement Study 191622-137 entitled, "*BOTOX in the treatment of urinary incontinence due to overactive bladder in patients 12 to 17 years of age"* was submitted on October 14, 2022, as a labeling supplement with clinical data. Allergan asserts that the study was not able to demonstrate a statistically significant difference in the primary endpoint of change from baseline in urinary incontinence episodes between the 100 unit or 50 unit dose group compared to the 25 unit dose group. Therefore, Allergan submitted the application to add the study data to Section 8.4 Pediatric section of the currently approved labeling.

3.2. Summary of Presubmission/Submission Regulatory Activity

January 18, 2013: BLA 103000, efficacy supplement 5251, was approved for the treatment of overactive bladder in adults who have inadequate response to or are intolerant of an anticholinergic medication with the following postmarketing requirements:

1) Study 191622-137: Initial double-blind single treatment base study to evaluate the safety and efficacy of intradetrusor injection of BOTOX for the treatment of overactive bladder with urinary incontinence in patients ≥12 to ≤ 17 years who have not been adequately managed with anticholinergic therapy.

2) Study 191622-138: Extension study to enroll all patients who complete the initial study. Patients in this study may be treated up to 48-weeks and may receive multiple re-treatments during that period to further evaluate the long-term safety and efficacy of BOTOX in the treatment of pediatric patients with overactive bladder and urinary incontinence.

May 30, 2013: The Sponsor submitted draft pediatric protocols for Study 191622-137 (also referred to as Study 137 in this review) and Study 191622-138 (also referred to as Study 138) to IND 012430.

October 31, 2013: Studies 137 and 138 were merged into one protocol, Study 191622-137: BOTOX in the treatment of urinary incontinence due to overactive bladder in patients 12 to 17 years of age.

February 8, 2019: A Deferral Extension request was granted on February 8, 2019, to change the final study report submission date from March 2019 to March 2022 due to difficulties with enrollment. The Sponsor submitted a Pediatric Deferral Extension Request for Study 191622-137 on October 5, 2018. At that time, only 48 of the planned 108 subjects had been enrolled since the start of the study in 2014. The Sponsor undertook an investigator survey that indicated the following reasons that potential patients did not enroll in the study: patient/parent uncomfortable about participating in research; patient/parent uncomfortable with minimally invasive procedure; patients did not meet eligibility criteria; parent/patient felt the visit schedule and procedures were too demanding; treatment available outside of study; and other reasons. The Sponsor planned to conduct motivational site visits and identify additional study sites in an effort to fulfill the PREA obligation.[9]

December 10, 2021: Type C Guidance Meeting, for IND 012430: Written responses were conveyed to the Sponsor in response to questions regarding challenges to date with Study 191622-137 and the acceptability of their proposal to end the study and to fulfill PREA. At this meeting, the Division (DUOG) recommended that the Sponsor stop further recruitment in Study 191622-137 and submit the data to date in an efficacy supplement.

Reviewer's Comment: *The Division held a Type C Guidance meeting with the Sponsor and, in response to their proposal to end the study and to fulfill PREA, provided Written Responses on 12/10/2021 agreeing with the Sponsor to stop further recruitment in Study 191622-137 and to submit the Final Study Report as a Labeling Supplement. The Sponsor has now submitted the data from Study 191622-137 in the current sBLA.*

[9] Study 191622-137 Deferral Extension Request Justification. BLA 103000 October 5, 2018.

February 11, 2022: Deferral Extension request granted to change the final study report submission from March 2022 to October 2022.

August 23, 2022: Type B, Pre-sBLA meeting for IND 012430: This meeting was requested by the Sponsor to discuss the format and content of the planned Labeling Supplement.

October 14, 2022: Labeling Supplement (SE-8) was submitted by the Sponsor to BLA 103000.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

No inspections were conducted during the course of review.

4.2. Product Quality

No changes in dosage form or formulation of BOTOX are proposed in this Labeling Supplement. Therefore, there are no chemistry, manufacturing, and controls data to review for this application. There are no changes in categorical exclusion category as no new indication is being approved and there is no significant increase in the use of the active moiety. See the quality memo in Panorama dated July 12, 2023.

From the chemistry, manufacturing, and controls perspective, this Labeling Supplement is recommended for approval of submitted changes made to Section 8.4 as negotiated by the Division.

4.3. Clinical Microbiology

Microbiology review was not necessary for this SE-8, Labeling Supplement.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There is no new nonclinical information submitted to support this supplement, and none is needed. Only clinical data were submitted with this supplement to support labeling changes to

Section 8.4 of PI. In addition, the Applicant proposes no labeling changes to nonclinical pharmacology/toxicology-related sections of the BOTOX United States Prescribing Information (Allergan 1989). From the nonclinical perspective, this Labeling Supplement is recommended for approval for the negotiated changes made to Section 8.4 of PI.

5.2. Referenced NDAs, BLAs, DMFs

Not applicable.

5.3. Pharmacology

Not applicable.

5.4. ADME/PK

Not applicable.

5.5. Toxicology

Not applicable.

6 Clinical Pharmacology

6.1. Executive Summary

The objective of this sBLA is to update the "Pediatric Use" subsection (Section 8.4) of the current BOTOX United States Prescribing Information (Allergan 1989) with results from pediatric Study 191622-137. Due to enrollment challenges, the study was terminated prior to reaching the planned target of 108 patients. The study was not able to demonstrate a statistically significant difference in the primary endpoint of change from baseline in urinary incontinence episodes between the 100 U or 50 U dose group when compared to the 25 U dose group (low dose comparator).

The Applicant did not propose any labeling changes to clinical pharmacology related sections. We reviewed and summarized the immunogenicity data from the clinical study in pediatric patients with OAB (Study 191622-137) in this unireview and we recommend approval of proposed/negotiated changes made to Section 8.4 of PI.

6.2. Summary of Clinical Pharmacology Assessment

The Applicant assessed immunogenicity in Study 191622-137 in pediatric patients with OAB. The study was a multicenter, randomized, double-blind, parallel-group, multiple-dose study to evaluate the efficacy and safety of BOTOX for the treatment of patients 12 to 17 years of age

with urinary incontinence due to OAB who had not been adequately managed with anticholinergic therapy. Patients were initially randomized in a 1:1:1 ratio to 1 of 3 treatment arms (25 U, 50 U, or 100 U BOTOX not to exceed 6 U/kg). A total of 55 subjects were treated in Study 191622-137, receiving 25 U (n=18), 50 U (n=17), or 100 U (n=20).

Of the 55 patients with evaluable samples in this study, 1 patient was positive for binding antibodies (BAB) at the baseline but was negative at all following timepoints. A total of 3 patients who were negative at study entry, developed BABs over the course of the study and none of them tested positive for neutralizing antibodies (NABs). With limited number of subjects who tested positive for BAB, no conclusion can be made regarding the impact of immunogenicity on efficacy or safety.

6.3. Clinical Pharmacology Questions

6.3.1. Immunogenicity

What was the incidence of BABs in the study population? Do the binding antibodies have neutralizing activity?

The incidence of BABs in pediatric OAB population was 5.5% (3/55) and nobody tested positive for NABs.

A total of 55 pediatric patients were treated in Study 191622-137. Blood samples for immunogenicity testing were collected on day 1 prior to Treatment Cycle 1, at Week 12 after the first treatment, prior to each subsequent treatment administration and at study exit. A total of 210 serum samples from 55 patients were analyzed for BABs.

Of the 55 patients with evaluable samples in this study, 1 patient was positive for binding antibodies at the baseline but was negative at all following timepoints. A total of 3 patients who were negative at study entry developed BABs over the course of the study: two patients were positive at the Treatment 3 visit, and 1 patient was positive at study exit. All postbaseline BAB positive patients became positive following administration of 100 U BOTOX. No BAB positive patients were positive for NABs.

A summary of immunogenicity results in Study 191622-137 is listed below in Table 3.

Table 3. Summary of Results for Patients Who Had a BAB Positive Sample in Study 191622-137

Patient ID	Dose Received / BAB Results / Titer / NAB Results	Treatment 1		Treatment 2		Treatment 3, pre-dose	Treatment 4, pre-dose	Study Exit
		Day 1, Baseline	Week 12	Pre-dose	Week 12			
(b) (6)	Dose Received BAB Results Titer NAB Results	100 Negative NA NA	NA Negative NA NA	100 Negative NA NA	No Sample[a]	100 Positive 5 Negative	No Sample[a]	No Sample[a]
	Dose Received BAB Results Titer NAB Results	50 Negative NA NA	No Sample[a]	100 Negative NA NA	NA Negative NA NA	100 Negative NA NA	No Sample[a]	NA Positive NR Negative
	Dose Received BAB Results Titer NAB Results	25 Positive 5 Negative	No Sample[a]	50 Negative NA NA	NA Negative NA NA	50 Negative NA NA	No Sample[a]	No Sample[a]
	Dose Received BAB Results Titer NAB Results	50 Negative NA NA	NA Negative NA NA	100 Negative NA NA	No Sample[a]	100 Positive 5 Negative	100 Negative NA NA	NA Negative NA NA

BAB = Binding Antibodies; NAB = Neutralizing Antibodies; NA = Not Applicable; NR = Not Reportable
a. Either no sample was received, or an insufficient volume was received
Cross reference: Listing 16.1.14-1, Listing 16.1.14-2

Source: Table 17 of Response to IR submitted on 05/30/23, SN0489
Abbreviations: BAB, binding antibodies; NAB, neutralizing antibodies

Does the immunogenicity affect efficacy and/or safety of the therapeutic protein?

Due to recruitment challenges, the study was terminated prior to reaching the proposed target of 108 patients, leading to a lack of power for the primary analyses (n = 55). The safety profile of BOTOX treatment for OAB in the pediatric population is consistent with clinical findings in the adult OAB population.

With limited number of subjects who tested positive for BAB, no conclusion can be made regarding the impact of immunogenicity on efficacy or safety.

6.3.2. Analytical Methods

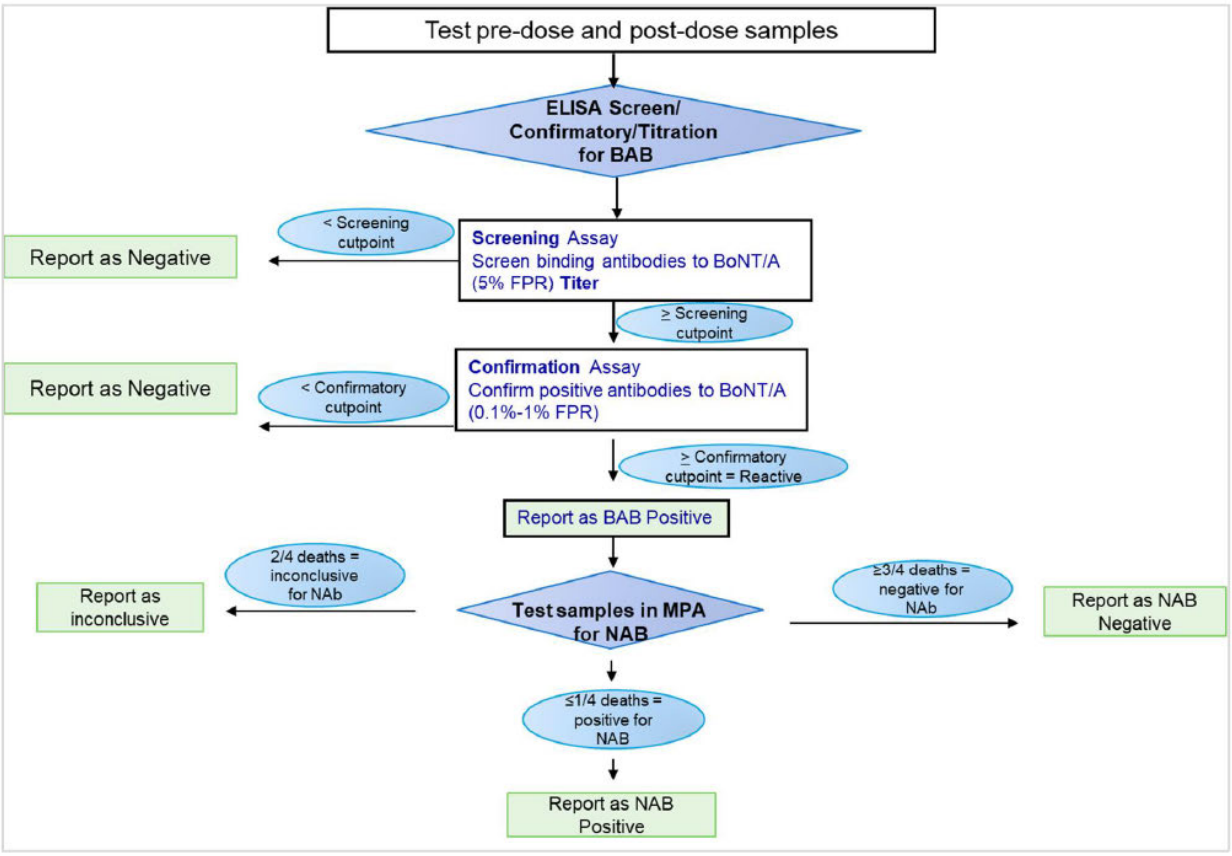
What bioanalytical methods are used to assess therapeutic protein concentrations?

Serum concentration of onabotulinumtoxinA was not measured. Using currently available analytical technology, it is not possible to detect BOTOX in the peripheral blood following intramuscular injection at the dose levels tested.

What bioanalytical methods are used to assess the immunogenicity potential of the product?

A two-step process was performed to assess binding antibodies and neutralizing antibodies in samples from the one pediatric trial (Figure 1). The process includes an enzyme-linked immunosorbent assay for binding antibodies and a mouse protection assay for neutralizing antibodies. First, results for serum BABs were analyzed using enzyme-linked immunosorbent assay and reported as negative, positive, or inconclusive for each patient with analyzable serum samples (i.e., sample collected and of sufficient quantity). Samples that were confirmed positive for BABs were subsequently tested for NABs using mouse protection assay (provided there was sufficient serum available to analyze). Results for serum NABs were reported as positive, negative, or inconclusive, and were summarized by dose and treatment cycle. According to reviewers from Office of Biotechnology Product, both binding and neutralizing antibody assays were adequately validated.

Figure 1. Immunogenicity Testing Strategy



Source: Figure 1 in Summary of Biopharm-ioab-rd220835-ped.pdf
Abbreviations: BAB: binding antibody; FPR: false positive rate; MPA: mouse protection assay; NAB: neutralizing antibody

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Sponsor submitted results from one phase 3 study, 191622-137, to support this sBLA.

Table 4. Summary of Individual Clinical Study

Study ID, Study Centers	Study Start Date, End Date Total Enrolled/ Planned	Study Design, Type of Control	Study Objectives	Study Drugs, Dose, Route, Regimen[1]	Duration of Treatment	Main Entry Criteria	Number of patients by Arm Enrolled/ Completed	Gender M/F Mean Age (Range)	Efficacy Endpoints[2]
191622-137 (Phase 3) 18 centers: US, UK, Canada, Australia, Belgium, Czech Republic, Italy, and Poland	Started: 23 May 2014 Completed: 10 Feb 2022 56/108	Phase 3 multi-center, randomized, double-blind, parallel-group, multiple-dose	To evaluate the safety and efficacy of BOTOX for the treatment of UI due to OAB in patients 12 to 17 years of age who had not been adequately managed with anti-cholinergic therapy	BOTOX 25 U, 50 U, or 100 U in a 1:1:1 ratio via 20 intradetrusor injections each of 0.5 mL	96 to 108 weeks	Patients ≥ 12 years to ≤ 17 years of age, with symptoms of OAB who had not been adequately managed by anti-cholinergics with ≥ 2 episodes of UI in 2-day diary during screening period	BOTOX 25 U: 19/12 BOTOX 50 U: 18/12 BOTOX 100 U: 19/9	14.5%/ 85.5% 14.0 years (12 to 17 years)	Primary: The number of daytime UI episodes as recorded in the 2-day bladder diary during the week preceding each study visit. The primary timepoint is Week 12 after treatment 1. Secondary: number of daytime micturition episodes, daytime urgency episodes, presence or absence of nighttime UI, volume voided per micturition, and time to patient request and time to patient qualification for retreatment. Other: Pediatric Incontinence Questionnaire score, modified TBS.

F = female; OAB = overactive bladder; M = male; TBS = Treatment Benefit Scale; UK = United Kingdom; US = United States; UI = urinary incontinence

1. Patients could receive multiple treatments dependent upon the number and timing of patient requests/qualification for retreatment.
2. For patients who receive multiple treatments in this study, the timepoint of focus is Week 12 after each treatment.

Source: Table 1: Summary of Individual Clinical Study; sBLA 103000/S-5325, SDN 8514, 2.7.3: Summary of Clinical Efficacy, page 8/39.

7.2. Review Strategy

Efficacy and safety datasets were reviewed for Study 191622-137. Safety data review also included case report narratives and case report forms. The locations of datasets submitted are:

\\CDSESUB1\evsprod\BLA103000\0468 contains the original submission, and \\CDSESUB1\evsprod\BLA103000\0474 contains updated efficacy results per FDA's request.

The efficacy review focused on individual response data from patient bladder diary parameters and clinical outcomes from Study 191622-137. The primary efficacy endpoint was the change from baseline to Week 12 post-treatment 1 in the daily average frequency of daytime urinary incontinence episodes based on Study 191622-137. The primary analysis population was the BOTOX treated group. Patients could elect to request additional BOTOX treatments only after Week 12 of treatment.

The Applicant's conclusions regarding efficacy were confirmed by independent FDA analysis of the data. FDA clinical and statistical reviewers collaborated throughout the review process. Disposition, demographics, and efficacy analyses in this review were performed by clinical and statistical review teams.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 191622-137: BOTOX in the Treatment of Urinary Incontinence Due to Overactive Bladder in Patients 12 to 17 Years of Age

Trial Design

Study 191622-137 was a phase 3, multicenter, randomized, double-blind, parallel-group, multiple-dose study designed to evaluate the efficacy and safety of three doses (25U, 50U and 100U) of BOTOX in pediatric patients 12 to 17 years of age with urinary incontinence due to OAB, who had not been adequately managed with anticholinergic therapy. The doses selected by the Sponsor for the pediatric study were intended to provide a sufficient range to assess dose-response while not exceeding the adult OAB dose of 100 U BOTOX.[10] Study 191622-137 did not have a placebo arm because the Sponsor considered inclusion of placebo not to be ethically justified. As a comparator, the lower dose of 25 U was included because this dose was

[10] Study 191622-137, protocol.

anticipated to be minimally effective, based on data previously obtained in the adult OAB Phase 2 Study, 191622-077.[11]

Eligible patients were randomized in a 1:1:1 ratio to one of the following three treatments (not to exceed 6 U/kg):

- 25 U BOTOX
- 50 U BOTOX
- 100 U BOTOX

Randomization was stratified by baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day bladder diary collection period). The study medication was administered via cystoscopy as 20 intradetrusor injections of 0.5 mL each. Injections were distributed evenly across the detrusor wall in the bladder and spaced approximately 1 cm apart, sparing the trigone.[12]

All patients were to receive prophylactic antibiotics prior to treatment administration. The treatment was to be administered to patients under general or local anesthesia. Patients had post-treatment follow-up clinic visits at Weeks 2, 6, and 12. After that, patients had alternating telephone and clinic follow-up visits every 6 weeks until the patient qualified for further retreatment or exited the study. Subjects could request retreatment starting from Week 12 after the previous study treatment. At retreatment, the investigator could either keep the dose the same or request a dose increase if the previous dose was well tolerated but there was an insufficient response. Subjects completed the study once 96 weeks from entry into the study at Day 1 had occurred, and at least 12 weeks follow-up since their last treatment.[13] The total duration of subject participation in the study was up to 108 weeks.

The investigator could elect to administer subsequent retreatments in a blinded fashion, either keeping the same dose or increasing the dose compared with the preceding treatment. The dose received by a patient could vary due to the dose limit of 6 U/kg (i.e., the dose was adjusted based on the patient's weight). In order to maintain blinding of the BOTOX dose received, the drug was reconstituted by an independent drug reconstitutor based on treatment assigned by interactive voice response system/ interactive web response system.

[11] Study 191622-137, Study Report, page 30/1413

[12] 191622-137 Synopsis, page 2/6.

[13] ibid

Inclusion Criteria

1) Male or female, aged 12 years to 17 years of age at the time of informed consent.
2) Patient has symptoms of OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by patient history.
3) Patient experiences a total of ≥ 2 episodes of daytime urinary urgency incontinence in the 2-day patient bladder diary completed during the screening period (daytime is defined as time between waking up to start the day and going to bed to sleep for the night).
4) Patient experiences urinary frequency, defined as an average of ≥ 8 micturitions (toilet voids) per day, i.e., a total of ≥ 16 micturitions in the 2-day patient bladder diary completed during the screening period.
5) Patient has not been adequately managed with 1 or more anticholinergic agents for the treatment of OAB in the opinion of the investigator. This includes patients who are still incontinent despite anticholinergic therapy, experiencing intolerable side effects, or are unwilling to continue to take the medication for any reason.
6) Patient is willing and able to use clean intermittent catheterization (CIC) to empty the bladder at any time after study treatment if it is determined to be necessary by the investigator.
7) Patient agrees to a minimum fluid intake of 1500 mL/m^2 body surface area per day, not to exceed 3000 mL/m^2 body surface area per day, during the patient bladder diary completion days at screening and prior to clinic visits during the study.

Exclusion Criteria

1) Patient has an uncontrolled systemic disease, previous or current diagnosis of malignancy.
2) Patient has symptoms of OAB due to any known neurological reason (e.g., spina bifida, spinal cord injury, or cerebral palsy).
3) Patient has a history of 2 or more UTIs treated with antibiotics within 6 months of randomization/Day 1 or is taking prophylactic antibiotics to prevent chronic UTI.
4) Patient has a history or evidence of any pelvic or urological abnormalities, except OAB, including:
    a) Bladder neck surgery resulting in an open bladder neck, or reconstructive surgery of the lower urinary tract (e.g., urostomy, urinary diversion, or bladder augmentation)
    b) Anatomical evidence of bladder outlet obstruction (including functional outlet obstruction), urethral or urethral valve obstruction/stricture at screening

c) Surgery of the urinary tract (including minimally invasive surgery) within 6 months of screening (except those listed above which are exclusionary for any time period)

d) Circumcision within 1 month of screening

e) Clinically relevant kidney abnormality, or clinically relevant vesicoureteric reflux, or disease of the bladder (other than OAB) that may affect bladder function

5) Patient has predominance of stress incontinence, or "giggle" incontinence, or any condition other than OAB that in the investigator's opinion may account for the patient being incontinent.
6) Patient has unmanaged, unresolved bowel problems (e.g., constipation, encopresis).
7) Patient uses CIC or an indwelling catheter to manage their OAB.
8) Patient has had previous or current botulinum toxin therapy of any serotype for any urological condition, or treatment with botulinum toxin of any serotype within 3 months of randomization/Day 1 for any other condition or use.
9) Patient has a postvoid residual (PVR) urine volume of > 40 mL at screening. The PVR measurement can be repeated once on the same day; the patient is to be excluded if the repeated measure is above 40 mL.
10) Patient has a daytime (waking hours) total volume of urine voided > 3000 mL, collected over one daytime period during the 2-Day bladder diary collection period prior to randomization/Day 1.[14]

Study Endpoints

The efficacy measures related to urinary symptoms of incontinence, frequency, urgency and volume per void were collected by the patient or parent/guardian on a 2-Day bladder diary in the week prior to each scheduled clinic visit (for baseline, the 2-Day diary could be collected at any time during the screening period).

The Applicant-defined primary efficacy endpoint was the change from baseline to Week 12 post-treatment 1 in the daily average frequency of daytime urinary incontinence episodes as

[14] Study 191622-137, Study Report Body.

recorded in the 2-day bladder diary. Daytime is defined as the time between waking up to start the day and going to bed to sleep for the night.

- The daily average frequency of daytime urinary incontinence episodes was obtained using the total number of daytime urinary incontinence episodes recorded in the 2-day bladder diary divided by 2, and
- Baseline frequency was defined as the daily average frequency of episodes of daytime urinary incontinence preceding the first study treatment.

Each daytime period recorded in the bladder diary was normalized to represent a 12-hour period to account for differing durations of the daytime period. On a given day, the number of daytime urinary incontinence episodes normalized to a 12-hour daytime period was calculated by:

(12/daytime period) X number of daytime urinary incontinence episodes

The final efficacy outcome is the average of the two days normalized results.

The Applicant-defined secondary efficacy measures included the following seven secondary efficacy endpoints assessed after each treatment[15]:

1) Responder analysis of the primary efficacy endpoint of daytime urinary incontinence, defined as at least 50% reduction from baseline in urinary incontinence
2) Change from baseline in daily average frequency of daytime micturition episodes
3) Change from baseline in daily average frequency of daytime urgency episodes
4) Presence or absence of nighttime urinary incontinence
5) Change from baseline in volume (mL) voided per micturition
6) Change from baseline in Pediatric Incontinence Questionnaire (PinQ) total score and item scores for 3 prespecified PinQ items (worry about smell, being with friends, and feel bad about myself)
7) Proportion of patients with a positive treatment response on the modified treatment benefit scale (TBS) (i.e., rating their condition "greatly improved" or "improved")

None of the secondary endpoints were prespecified in the protocol as a “key secondary endpoint” for assessment in the overall study testing.

[15] Study report body: pages 35-36/1413

Statistical Analysis Plan

Analysis Populations

BOTOX-Treated Population: All patients enrolled into the study who received at least one BOTOX treatment were included. All efficacy and safety analyses in the study was based on the BOTOX-Treated Population.

Sample Size Consideration

There was no formal sample size calculation. The original proposed sample size was 108. However, due to recruitment challenges, a total of only 56 patients were enrolled in the study.

Analysis of Primary Efficacy Endpoint

Hypothesis: for each of the BOTOX doses of 100 U and 50 U,

- The null hypothesis (H0) states that there is no difference between that dose group and the 25 U BOTOX dose group in mean change from baseline in daily average frequency of daytime urinary incontinence episodes at Week 12 post-treatment 1.
- The alternative hypothesis (H1) states that there is a difference in mean change from study baseline in daily average frequency of daytime urinary incontinence episodes between that BOTOX dose group and the 25 U dose group at Week 12 post-treatment 1.

The hypotheses were tested using an analysis of covariance model with baseline value as covariate and treatment group as a factor.

Multiplicity adjustment: A hierarchical analysis strategy to adjust for multiplicity was specified in the protocol. The test order is

1) 100 versus 25 U of BOTOX, and
2) 50 versus 25 U of BOTOX.

Treatment group differences at Week 12 were tested at the 0.05 significance level in a fixed sequence fashion. Results of hypothesis testing for 50 U versus 25 U of BOTOX were considered for statistical significance **only if** the treatment difference for 100 U versus 25 U of BOTOX was shown to be statistically significant.

Missing value imputation: Last observation carried forward (LOCF) imputation was applied to missing values up to 12 weeks after first study treatment. No imputation was done for missing values on visits after the post-treatment 1 Week 12 visit.

In contrast to LOCF, mixed-effect model repeated measures analysis (MMRM) (Mallinckrodt et al. 2001a; Mallinckrodt et al. 2001b) was conducted on the primary efficacy variable with the observed data. The data included all the observed cases up to and including the primary

timepoint (Week 12 after the first treatment). The unstructured variance-covariance structure was used in the model. A sensitivity analysis using MMRM allowed for estimation of patient's missing response by using all the observed data and nonconstant correlations among the timepoints.

Subgroup Analyses for Primary Efficacy Endpoint: The following baseline factors were used for the subgroup analyses:

- Baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 versus > 6)
- Race (Caucasian or non-Caucasian)
- Sex (male or female)
- Region (North America versus Other Regions).
  - North America=U.S.A and Canada,
  - Other Regions=Australia, Belgium, Czech Republic, Great Britain, Italy, and Poland.

Analysis of Secondary Efficacy Endpoints: The main focus of this review was to analyze the primary efficacy endpoint. The statistical reviewer did not analyze the secondary efficacy endpoints because they were all exploratory.

Protocol Amendments

There were two protocol amendments to the original protocol (dated 24 February 2014).

Protocol Amendment #1

The first amendment was dated 27 February 2014. The main change was to provide clarification in Section 5.5 (Method for Assignment to Treatment Groups/Randomization) and Section 7 (Statistical Procedures). In addition, the wording of Section 8.7 (Early Discontinuation of Patients) was modified. This amendment represents the initial protocol for use in this study.

Protocol Amendment #2

The second amendment was dated 23 September 2014. The main changes included:

- Addition of an exclusion criterion regarding medical conditions that may put patients at increased risk with exposure to BOTOX;
- The wording of the exclusion criterion regarding history or evidence of any pelvic or urological abnormalities was clarified to include further examples (i.e., clinically relevant vesicoureteric reflux or disease of the bladder) and reconstructive surgery (i.e., bladder augmentation);
- Addition of an exclusion criterion regarding medical conditions (hemophilia, or other clotting factor deficiencies, or disorders that cause bleeding diathesis);

- Addition of an exclusion criterion regarding patients who cannot withhold any antiplatelet, anticoagulant therapy, or other medications with anticoagulant effects for 3 days prior to randomization/day 1.

In addition, the following updates were made:

- Aligned criteria for primary analysis to be consistent with Section 7 (Statistical procedures); Clarified that the confidence interval (CI) for the difference of 2 means was based on normal distribution for the purpose of the sample size calculation;
- Clarified the usage of medications for nocturia/nocturnal enuresis (i.e., desmopressin) and other medications for OAB (e.g., mirabegron) and their washout periods;
- Clarified the exclusion criterion regarding usage of psychiatric medications or medications for attention deficit hyperactivity to indicate that patients need to have been on a stable dose prior to study entry rather than for 6 months prior;
- Added criterion regarding PVR urine volume to be < 200 mL for patients to qualify for retreatment. (previously this was only mentioned in Section 5.10.1);
- Clarified that the PVR value obtained at qualification for retreatment must be confirmed to have been < 200 mL for the "day of treatment criteria" to be met;
- Clarified that the urinalysis, culture, and sensitivity procedures were to be performed at all clinic visits;
- Added fluid dispensing connector (for reconstitution of study drug) to other study supplies;
- Clarified that if a patient had missing values at all scheduled posttreatment visits, the baseline value would be carried forward;
- Clarified that events considered to be either new or worsening of anticipated clinical signs or symptoms collected as clinical efficacy variables and related to the underlying disease of OAB should not be collected adverse events unless the disease progression was greater than anticipated in the natural course of the disease.[16]

Conduct of the Study

There were challenges enrolling patients with OAB in the 12 to 17 year age group. These challenges included the low prevalence of OAB in this age group, as well as patients/parents being uncomfortable with the minimally invasive procedure and/or about participating in research, and those who were not satisfied with oral therapy.

[16] Study 191622-137 Protocol and Protocol Amendments

As a result of these enrollment issues, after agreement with the Agency, the study was terminated prior to reaching the initial enrollment target of 108 patients. A total of 56 patients were randomized, 55 of whom received at least 1 dose of study drug.

Because of the early termination, an analysis was performed when all enrolled patients exited the study and results from this analysis were presented in the final clinical study report. The hierarchal testing strategy described in the protocol was not implemented, i.e., there was no multiplicity adjustment for two tests for the primary efficacy endpoint.

The number of subjects enrolled by year shows the difficulty of enrollment (Table 5 below).

Table 5. Number of Subjects Enrolled by Year for Study 191622-137

Year	2014	2015	2016	2017	2018	2019	2020	2021	Total
Number of enrolled	8	22	13	4	1	5	2	1	56

Source: statistical reviewer

8.1.2. Study Results

Baseline Demographic Characteristics

These baseline demographic analyses are based on the dose subjects actually received in cycle 1 treatment.

Demographic and baseline characteristics were generally balanced among the three treatment groups except that the 50 U group had no male subjects. The overall mean age was 14.0 years (12 to 17), and the majority of subjects were female (85.5%) and white (74.5%). The median baseline weight, height, and body mass index of patients were 59.1 kg, 160.5 cm, and 22.3, respectively, and were similar across the three arms. Only 4 (7.3%) patients were enrolled from the United States. Demographic and baseline characteristics of subjects enrolled in study 191622-137 are summarized in Table 6.

Table 6. Baseline Demographics for Study 191622-137 (BOTOX-Treated Population)

Characteristic	BOTOX25	BOTOX50	BOTOX100	Total
N	**18**	**17**	**20**	**55**
Gender				
Female	16 (88.9%)	17 (100.0%)	14 (70.0%)	47 (85.5%)
Male	2 (11.1%)	0 (0%)	6 (30.0%)	8 (14.5%)
Race				
White	12 (66.7%)	12 (70.6%)	17 (85.0%)	41 (74.5%)
Asian	(0%)	1 (5.9%)	(0 %)	1(1.8%)
Not Reported	2 (11.1%)	1(5.9%)	1(5.0%)	4(7.3%)
Other	1 (5.6%)	1(5.9%)	1(5.0%)	3(5.5%)
Unknown	3 (16.7%)	2(11.8%)	1(5.0%)	6(10.9%)
Age (Year)				
Mean (SD)	13.7 (1.49)	14.3 (1.86)	14.0 (1.75)	14.0 (1.69)
Median	13.0	14.0	14.0	14.0
Range (Min, Max)	(12, 17)	(12, 17)	(12, 17)	(12, 17)

Characteristic	BOTOX25	BOTOX50	BOTOX100	Total
N	**18**	**17**	**20**	**55**
Age Category 1				
12 years	4(22.2%)	4(23.5%)	7(35.0%)	15(27.3%)
13 years	6(33.3%)	3(17.6%)	1(5.0%)	10(18.2%)
14 years	2(11.1%)	3(17.6%)	3(15.0%)	8(14.5%)
15 years	4(22.2%)	(%)	4(20.0%)	8(14.5%)
16 years	1(5.6%)	5(29.4%)	4(20.0%)	10(18.2%)
17 years	1(5.6%)	2(11.8%)	1(5.0%)	4(7.3%)
Weight (Kg) at Baseline				
Mean (SD)	61.1 (20.33)	57.5 (16.42)	62.0 (17.55)	60.3 (17.91)
Median	61.4	60.0	57.5	59.1
Range (Min, Max)	(31.7, 108.1)	(30.0, 90.8)	(37.0, 108.2)	(30.0, 108.2)
Height (cm) at Baseline				
Mean (SD)	160.3 (9.59)	162.2 (8.74)	159.8 (7.36)	160.7 (8.47)
Median	160.5	163.0	158.0	160.5
Range (Min, Max)	(141, 175)	(144, 176)	(141.9, 173)	(141, 176)
BMI at Baseline				
Mean (SD)	23.39 (6.502)	21.53 (4.858)	24.04 (5.382)	23.05 (5.623)
Median	22.28	21.80	23.04	22.32
Range (Min, Max)	(14.57, 42.21)	(14.47, 33.15)	(17.75, 36.45)	(14.47, 42.21)
Region				
North America	5(27.8%)	6(35.3%)	4(20.0%)	15(27.3%)
Other Regions	13(72.2%)	11(64.7%)	16(80.0%)	40(72.7%)
Country				
AUS	3(16.7%)	(%)	(%)	3(5.5%)
BEL	4(22.2%)	1(5.9%)	5(25.0%)	10(18.2%)
CAN	3(16.7%)	5(29.4%)	3(15.0%)	11(20.0%)
CZE	(%)	(%)	2(10.0%)	2(3.6%)
GBR	5(27.8%)	8(47.1%)	7(35.0%)	20(36.4%)
ITA	(%)	1(5.9%)	(%)	1(1.8%)
POL	1(5.6%)	1(5.9%)	2(10.0%)	4(7.3%)
USA	2(11.1%)	1(5.9%)	1(5.0%)	4(7.3%)

Source: Stats Review Team
Abbreviations: AUS, Australia; BEL, Belgium; BMI, Body Mass Index; CAN, Canada; CZE, Czech Republic; GBR, Great Britain; ITA, Italy; max, maximum; min, minimum; POL, Poland; SD, Standard Deviation; USA, United States of America

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

These baseline disease characteristics analyses are based on the dose the subject received in cycle 1 treatment.

Subjects in the 25 U arm experienced more mean daily episodes of daytime urinary incontinence at baseline (5.29) than those in the 50 U and 100 U BOTOX arms (3.54 and 3.64, respectively). Similar findings were observed with the mean of daily frequency of urinary urgency, the mean daily frequency of daytime urinary urgency incontinence, the mean daily frequency of daytime urinary urgency incontinence episodes, and the mean daily frequency of daytime micturition episodes at baseline.

Overall, at baseline, the mean postvoid residual urine volume was 11.13 mL. The subjects in the 50 U arm had more residual volume at baseline (18.68 mL) than those in the 25 U and 100 U

BOTOX arms (7.01 mL and 8.41 mL, respectively). The overall mean duration of OAB was 3.28 years and this were similar across the three arms.

Table 7. Baseline and Disease Characteristics for Study 191622-137 (BOTOX-Treated Population)

Characteristic	BOTOX25	BOTOX50	BOTOX100	Total
N	**18**	**17**	**20**	**55**
Stratification Factor				
UIGT6[1]	9 (50.0%)	7 (41.2%)	8 (40.0%)	24 (43.6%)
UILE6	9 (50.0%)	10 (58.8%)	12 (60.0%)	31 (56.4%)
Daily Freq of Daytime Urinary Incontinence Episodes (standardized by 12 hours)				
Mean (SD)	5.29 (3.447)	3.54 (2.696)	3.64 (2.951)	4.15 (3.100)
Median	4.15	3.00	2.35	3.10
Range (Min, Max)	(1.7, 12.6)	(1.1, 12.6)	(0.4, 10.4)	(0.4, 12.6)
Daily Freq of Daytime Urinary Urgency Episodes (standardized by 12 hours)				
Mean (SD)	7.52 (4.486)	5.42 (2.722)	4.42 (2.573)	5.74 (3.548)
Median	7.00	4.70	3.90	4.70
Range (Min, Max)	(0.9, 20.5)	(1.3, 9.1)	(1.3, 11.1)	(0.9, 20.5)
Daily Freq of Daytime Urinary Urgency Incontinence Episodes (standardized by 12 hours)				
Mean (SD)	3.99 (2.927)	2.72 (2.028)	2.65 (2.475)	3.11 (2.541)
Median	2.90	2.50	2.05	2.50
Range (Min, Max)	(0.9, 12.1)	(0.5, 9.1)	(0.0, 10.4)	(0.0, 12.1)
Daily Freq of Daytime Micturition Episodes (standardized by 12 hours)				
Mean (SD)	11.16 (4.217)	8.45 (1.968)	8.06 (2.500)	9.19 (3.299)
Median	9.50	7.90	8.30	8.60
Range (Min, Max)	(5.5, 21.0)	(6.4, 13.5)	(0.0, 11.9)	(0.0, 21.0)
Volume Voided per Micturition (mL)				
Mean (SD)	165.29 (72.831)	225.15 (72.973)	187.94 (77.224)	192.03 (77.044)
Median	149.20	231.30	158.20	180.00
Range (Min, Max)	(70.1, 300.0)	(127.1, 362.2)	(96.6, 412.5)	(70.1, 412.5)
Duration of OAB (years)				
n	8	14	14	36
Mean (SD)	3.19 (2.794)	3.73 (3.051)	2.89 (2.788)	3.28 (2.837)
Median	1.90	3.20	1.35	1.55
Range (Min, Max)	(1.0, 8.7)	(1.0, 10.4)	(0.4, 7.9)	(0.4, 10.4)
Postvoid Residual Urine Volume (mL)				
Mean (SD)	7.01 (7.348)	18.68 (11.281)	8.41 (9.564)	11.13 (10.642)
Median	5.00	21.00	5.90	9.00
Range (Min, Max)	(0.0, 24.0)	(0.0, 35.0)	(0.0, 34.0)	(0.0, 35.0)

Source: statistical reviewer

[1]: **UIGT6** stands for the total baseline daytime urinary urgency incontinence episodes over the 2-day bladder diary collection period is greater than 6 episodes; and **UILE6** stands for the total baseline daytime urinary urgency incontinence episodes over the 2-day bladder diary collection period is less than or equal to 6 episodes. These values were from the randomization stratification.
Abbreviations: max, maximum; min, minimum; OAB, overactive bladder; SD, standard deviation

Efficacy Results – Primary Endpoint

- Primary efficacy endpoint results: the change from baseline to Week 12 post-treatment 1 in the daily average frequency of daytime urinary incontinence episodes were presented in this section. Although some subjects received more than one treatment, efficacy results after Week 12 post-treatment 1 were not reviewed.
- The statistical reviewer noticed that one subject (usubjid= (b) (6)) was randomized to the 25 U arm, however, the patient received 100 U. The efficacy analyses presented in the clinical study report were based on the treatment doses that subjects received, not based on the treatment groups randomized as it should have been for the efficacy analyses. Per FDA's request, the Applicant did submit the updated primary efficacy analysis results based on the treatment groups randomized (SN 0474 dated on Dec. 13, 2022).

Study 191622-137 demonstrated no statistically significant difference when 100 U, or the 50 U BOTOX dose groups were compared to the 25 U BOTOX dose group at Week 12 after treatment 1. The efficacy analysis population consisted of the BOTOX-treated population, n=55. [17]

The primary efficacy variable is the change from baseline to Week 12 post-treatment 1 in the daily average frequency of daytime urinary incontinence episodes.

At Week 12 of Cycle 1 (primary timepoint), the least square mean change in daytime urinary incontinence episodes was -1.33, -0.97, and -2.44, in the 25 U, 50 U and 100 U BOTOX groups, respectively.

The summary analysis of the primary efficacy endpoint is displayed in Table 8.

These results are similar to the results using MMRM approach (See Table 22 in the Appendix)

Table 8. Analysis of Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes LOCF Imputation Applied to Missing Values up to Week 12, Treatment Cycle 1 for Study 191622-137 (BOTOX-Treated Population)

Analysis Visit Statistics	BOTOX 25U (N=19)	BOTOX 50U (N=17)	BOTOX 100U (N=19)
Baseline			
Mean (SD)	5.11 (3.450)	3.54 (2.696)	3.74 (2.995)
Median	4.10	3.00	2.40
Q1, Q3	2.90, 6.10	2.20, 3.50	1.40, 5.40
Min, Max	1.7, 12.6	1.1, 12.6	0.4, 10.4
n	19	17	19

[17] 191622-137, Synopsis, page 5/6.

Analysis Visit Statistics	BOTOX 25U (N=19)	BOTOX 50U (N=17)	BOTOX 100U (N=19)
Week 2			
Mean (SD)	1.92 (2.392)	2.06 (2.632)	1.98 (2.740)
Median	0.90	1.00	0.90
Q1, Q3	0.00, 2.70	0.00, 3.10	0.00, 2.60
Min, Max	0.0, 8.7	0.0, 8.6	0.0, 8.7
n	19	17	19
Change from baseline			
Mean (SD)	-3.18 (2.633)	-1.48 (3.934)	-1.76 (2.045)
Median	-3.00	-1.30	-1.40
Q1, Q3	-4.20, -1.50	-2.50, -0.10	-2.30, -0.40
Min, Max	-9.9, 1.0	-12.6, 7.4	-8.0, 1.9
n [1]	19	17	19
95% CI [2]	(-4.453, -1.915)	(-3.499, 0.546)	(-2.743, -0.772)
P-value [2]	<0.0001	0.1413	0.0015
Least square estimates [3]			
Mean (SE)	-2.61 (0.537)	-1.84 (0.562)	-2.00 (0.530)
95% CI	(-3.689, -1.531)	(-2.973, -0.716)	(-3.066, -0.938)
P-value	<0.0001	0.0019	0.0004
vs. BOTOX 25U			
Difference (SE)		0.77 (0.786)	0.61 (0.760)
95% CI		(-0.812, 2.343)	(-0.918, 2.135)
P-value		0.3346	0.4275
Week 6			
Mean (SD)	2.53 (3.838)	1.65 (2.286)	2.13 (3.543)
Median	1.10	1.00	0.80
Q1, Q3	0.40, 3.20	0.00, 1.90	0.00, 2.10
Min, Max	0.0, 16.2	0.0, 7.7	0.0, 13.2
n	19	17	19
Change from baseline			
Mean (SD)	-2.58 (3.207)	-1.88 (3.562)	-1.61 (2.079)
Median	-2.90	-1.60	-1.60
Q1, Q3	-5.20, -1.20	-2.50, -1.10	-2.30, -0.60
Min, Max	-8.7, 4.1	-12.6, 4.8	-7.3, 2.8
n [1]	19	17	19
95% CI [2]	(-4.125, -1.033)	(-3.714, -0.051)	(-2.613, -0.608)
P-value [2]	0.0025	0.0446	0.0034
Least square estimates [3]			
Mean (SE)	-2.21 (0.647)	-2.12 (0.676)	-1.77 (0.637)
95% CI	(-3.505, -0.909)	(-3.479, -0.764)	(-3.049, -0.489)
P-value	0.0013	0.0028	0.0077
vs. BOTOX 25U			
Difference (SE)		0.09 (0.945)	0.44 (0.915)
95% CI		(-1.812, 1.983)	(-1.399, 2.274)
P-value		0.9285	0.6344
Week 12			
Mean (SD)	3.16 (3.755)	2.95 (4.470)	1.56 (1.692)
Median	2.60	1.40	0.60
Q1, Q3	0.50, 3.40	0.50, 2.90	0.40, 2.70
Min, Max	0.0, 15.7	0.0, 15.2	0.0, 5.2
n	19	17	19

Analysis Visit Statistics	BOTOX 25U (N=19)	BOTOX 50U (N=17)	BOTOX 100U (N=19)
Change from baseline			
Mean (SD)	-1.94 (3.522)	-0.58 (5.480)	-2.18 (1.742)
Median	-1.40	-1.30	-2.00
Q1, Q3	-3.80, 0.10	-2.10, -0.50	-3.40, -1.40
Min, Max	-10.0, 4.7	-12.6, 14.0	-5.4, 2.3
n [1]	19	17	19
95% CI [2]	(-3.640, -0.244)	(-3.400, 2.235)	(-3.018, -1.339)
P-value [2]	0.0272	0.6671	<0.0001
Least square estimates [3]			
Mean (SE)	-1.33 (0.773)	-0.97 (0.809)	-2.44 (0.762)
95% CI	(-2.887, 0.218)	(-2.596, 0.651)	(-3.968, -0.907)
P-value	0.0905	0.2347	0.0024
vs. BOTOX 25U			
Difference (SE)		0.36 (1.131)	-1.10 (1.094)
95% CI		(-1.908, 2.632)	(-3.299, 1.093)
P-value		0.7502	0.3179

Source: Statistical Reviewer
[1] Number of subjects in the analysis;
[2] 95% CI and P-value from paired t-test of within-group mean change from baseline;
[3] Least square estimates and difference vs. control arm (BOTOX 25U) are based on ANCOVA model with baseline and treatment arm in the model. All the models, baseline covariate is statistically significant.
Abbreviations: CI, confidence interval; max. maximum; min, minimum; SD, standard deviation; SE, standard error

Statistical Reviewer Comment*: A supporting analysis was performed using MMRM that yielded similar results and the same conclusion. For a detailed review of the MMRM analysis, see the table in the Appendix.*

Subgroup analyses of the primary efficacy endpoint performed by baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 and >6 in 2-day collection period), gender (female), and race (white) resulted in similar conclusion to the overall summary. Please see Tables in Appendix for details.

At the request of the Agency, the Applicant conducted the primary efficacy analysis based on the treatment groups randomized, since one subject was randomized to the 25 U arm but received 100 U. The new tables generated did not change any conclusions provided in the sBLA.

Cross-Discipline Team Leader (CDTL) Comments: *The primary efficacy endpoint did not demonstrate a statistically significant difference when the 100 unit BOTOX dose was compared to the 25 unit BOTOX dose and when the 50 unit BOTOX dose was compared to the 25 unit BOTOX dose. The statistical reviewer from the Office of Biostatistics has confirmed these results. These results will be summarized in Section 8.4 of PI.*

Compliance With Good Clinical Practices

The Applicant attested to compliance with good clinical practice for the submitted study in accordance with the International Council on Harmonization guidelines and with 21 CFR parts 50, 56, and 312.

Financial Disclosure

Financial disclosure was made for the required study submitted to this application. There is no evidence to suggest that a financial relationship had any impact on study results. The Applicant/Sponsor submitted a Financial Certification and Disclosure (Section 1.3.4) for Study 191622-137. A list of investigators certifying the absence of financial interests and arrangements was submitted. The Applicant/Sponsor certified that (1) no financial arrangements with an investigator have been made where study outcome could affect compensation; (2) the investigator does not have a proprietary interest in the tested product; (3) the investigator did not have an equity interest in the Sponsor; and (4) the investigator did not receive payments of other sorts.

Patient Disposition

The study included male and female patients 12 to 17 years of age with OAB and urinary incontinence. A total of 68 patients were screened at 20 sites and a total of 56 patients were enrolled and randomized into Study 191622-137. Of these, 55 patients received at least 1 dose of the study medication: 19, 17, and 19 patients were assigned to 25 U BOTOX, 50 U BOTOX, and 100 U BOTOX, respectively. One patient in the 50 U BOTOX group was randomized but did not receive treatment.[18] 55 patients were included in BOTOX-treated population for analysis. 33 patients (58.9%) completed Study 191622-137. 23 of the 56 enrolled patients discontinued from the study early. Of the discontinued patients, 7 were in the BOTOX 25U group, 6 were in the BOTOX 50 U group, and 10 were in the BOTOX 100 U group. Reasons for discontinuation included: lack of efficacy (n = 6), lost to follow-up (n = 4), withdrawal by patient (n = 3), adverse event (n = 1), and other (n = 9).[19]

Reviewer's Comment: *Other reasons for discontinuation were reviewed by this reviewer and did not appear to be safety-related.*

One patient in the BOTOX 100 U group discontinued the study due to a treatment-emergent adverse event (TEAE), an event of vesicoureteric reflux during treatment Cycle 2 that was not considered related to study drug by the investigator.[20]

Reviewer's Comment*: Concur with the investigator's finding.*

Among 55 patents who were treated during cycle 1, 46 (84%) went on to cycle 2 treatment phase. Subject disposition is summarized in Table 9.

[18] 191622-137, Clinical Study Report, page 41/1413.

[19] ibid

[20] ibid, page 73/1413.

Table 9. Study 191622-137 Patient Disposition (All Screened Patients)

Disposition	BOTOX 25U n (%)	BOTOX 50U n (%)	BOTOX 100U n (%)	Total n (%)
Screened				68
Randomized	19 (100.0)	18 (100.0)	19 (100.0)	56 (100.0)
Treated **(planned treatment)**	**19**	**17**	**19**	**55 (98.2%)**
Completed the study	12 (63.2)	12 (66.7)	9 (47.4)	33 (58.9)
Discontinued from study	7 (36.8)	6 (33.3)	10 (52.6)	23 (41.1)
Reasons of discontinuation				
Adverse event		1		1
Lack of efficacy	2	1	3	6
Lost to follow-up	1	1	2	4
Withdrawal by subject		1	2	3
Other	**4**	**2**	**3**	**9**
Treatment Cycle 1				
Treated (actually received)	18 (100.0)	17 (100.0)	20 (100.0)	55 (100.0)
Completed study in cycle 1 treatment	2	2	2	6
Entered cycle 2	**15** (83.3)	**14** (82.4)	**17** (85.0)	**46** (83.6)
Discontinued from study during cycle 1	1 (5.6)	1 (5.9)	1 (5.0)	3 (5.5)
Reasons of discontinuation				
Lack of efficacy			1	1
Withdrawal by subject		1		1
Other	1			1
Treatment Cycle 2				
Treatment actually received in cycle 2	**1**	**17**	**28**	**46**

Source: statistical reviewer

Protocol Violations/Deviations

The reported protocol deviations are listed in Table 10.

Table 10. Number (%) of Patients With Significant Protocol Deviations – All Randomized or Treated Patients

Protocol Deviation Standard Text	BOTOX 25 U (N=19) n (%)	BOTOX 50 U (N=18) n (%)	BOTOX 100 U (N=19) n (%)	Total (N=56) n (%)
Overall	10 (52.6)	9 (50.0)	8 (42.1)	27 (48.2)
Daytime total volume of urine voided > 3000 mL during screening	2 (10.5)	0 (0.0)	0 (0.0)	2 (3.6)
Initiation of prohibited Medication/Treatment after randomization to Week 12	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.8)
Did not discontinue anticholinergics or other medications or therapies to treat OAB, for the minimum required time	2 (10.5)	1 (5.6)	0 (0.0)	3 (5.4)
Experienced < 16 episodes of daytime urinary frequency in the 2-day bladder diary completed at screening	0 (0.0)	0 (0.0)	1 (5.3)	1 (1.8)
Experienced < 2 episodes of daytime urinary urgency incontinence in the 2-day bladder diary at screening	0 (0.0)	1 (5.6)	1 (5.3)	2 (3.6)
Had UTI on day of treatment	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.8)
Has had previous or current botulinum toxin therapy of any serotype for any urological condition	0 (0.0)	0 (0.0)	1 (5.3)	1 (1.8)
Randomized but never received treatment	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.8)
Randomized into incorrect stratum and administered Ip	3 (15.8)	5 (27.8)	4 (21.1)	12 (21.4)
Study Medication not injected per protocol at treatment	1 (5.3)	3 (16.7)	1 (5.3)	5 (8.9)
Study medication not reconstituted according to the protocol	3 (15.8)	1 (5.6)	0 (0.0)	4 (7.1)

OAB = overactive bladder; UTI = urinary tract infection

Cross reference: Table 14.1-2.1

Source: 191622-137 study report body, Table 4, page 44/1413

There were 12 protocol deviations in which the subject was randomized into the incorrect stratum and administered the investigational product. Therefore, the resultant mis-stratification may have led to an imbalance in some of the baseline characteristics between the treatment arms.

There were four cases in which the study medication was not injected per protocol. In one case, there was an extra injection given, while the correct volume was administered, and in three cases the investigational product was injected into the bladder wall and/or bladder dome.

There were 5 instances in which the study medication was not reconstituted per protocol and resulted in a dosing error. In Treatment Cycle 1, one patient was randomized to 25 U BOTOX but received 100 BOTOX, and in the second cycle, the same patient was intended to receive 50 U BOTOX but received 100 U BOTOX. A second patient was intended to receive 25 U but received 100 U BOTOX in cycle 2. A third patient was intended to receive 50 U but received 100 U BOTOX in cycle 2. A fourth patient was intended to receive 100 U but received 50 U BOTOX in cycle 2.

In cycle 1, one patient (usubjid=[redacted]) who got the wrong dose in 1st treatment cycle was randomized to 25U arm but received 100U. The subject was included into randomized treatment group for efficacy analyses which is different from safety analyses.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The stated study objective was to evaluate the safety and efficacy of BOTOX for the treatment of urinary incontinence due to OAB in patients 12 to 17 years of age who have not been

adequately managed with anticholinergic therapy. One of the main inclusion criteria for the study was that a patient had not been adequately managed with 1 or more anticholinergic agents for the treatment of OAB in the opinion of the investigator. This included patients who were still incontinent despite anticholinergic therapy, experiencing intolerable side effects, or were unwilling to continue to take the medication for any reason. Anticholinergic therapy had been used by all patients prior to study enrollment. There were three patients who did not discontinue anticholinergics or other medications or therapies to treat OAB for the minimum required time. No rescue medication was used during the clinical trial.

Reviewer's Comment: *Treatment compliance was adequate.*

Data Quality and Integrity

The submission contains all required components of the electronic common technical document (eCTD). The overall quality and integrity of the application appear to be acceptable. Requests for additional information from the Applicant throughout the review process were addressed in a timely fashion.

There were a few minor issues identified during the review process regarding the Analysis Dataset Model datasets, Subject-Level Analysis Dataset (ADSL) and Diary Data Analysis Dataset (ADDI).

In the SAS program submitted for generating ADSL from raw data sets, it appears that two data sources, raw.kit and raw.rd_unit_dose, were used to generate ADSL, while these two data sources were not submitted. These did not prevent the reviewer from checking the ADSL.

In the ADDI dataset, there were four subjects with missed urinary leaking frequency measure at Week 2 without any imputation. It appears that the SAS program used to generate this dataset had glitches. However, it did not affect our review.

Efficacy Results – Secondary and Other Relevant Endpoints

Due to the early termination of the study with the resultant small sample size and nonsignificant results for primary efficacy endpoint, the statistical reviewer did not conduct any analyses for the secondary efficacy endpoints.

Exploratory COA (PRO) Endpoints

The Clinical Outcome Assessment (COA)-related secondary efficacy endpoints in the study include:

- Change in PinQ total score, and item scores for 3 PinQ items
- Proportion of patients with a positive response at Week 12 in modified TBS

Review Summary

A consult was submitted to the Division of Clinical Outcome Assessment. The following are their conclusions in response to the consult request:

The Applicant did not submit an evidence dossier to support that the PinQ and modified TBS are fit-for-purpose for the context of this development program. In the absence of supportive evidence related to the PinQ and modified TBS, there is insufficient information to fully review and comment on these instruments.

Key Issues Identified

1) *Lack of qualitative and quantitative evidence to support the content validity and other measurement properties of the PinQ and modified TBS.*
2) *Patient reported outcome (PRO) data did not achieve statistical significance in the prespecified endpoints.*
3) *Due to the lack of statistical significance, it is unlikely the PRO data demonstrate a clinically meaningful benefit.*
    a) *Lack of evidence to support what constitutes a clinically meaningful improvement in PRO scores.*
    b) *Lack of anchor scales to help interpret the clinical meaningfulness of the PRO Endpoints. However, we recognize that the small sample size posed challenges with interpretation of any conducted anchor-based analyses for the context of this development program.*

CDTL Comment: *The secondary endpoints were not pre specified and were measured only for exploratory reasons as noted by the Clinical Reviewer above. Therefore, these are not labeled.*

Dose/Dose Response

The study was designed to compare the 2 doses of 50 U, and 100 U BOTOX to 25 U BOTOX. Study 191622-137 did not demonstrate a dose response curve across the 50 U, and 100 U BOTOX dose groups.[21]

Durability of Response

Not applicable.

[21] Study 191622-137 Study Report, page 69/1413.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

None.

8.1.3. Assessment of Efficacy Across Trials

Supplemental BLA 103000/S-5325 consisted of only one study which did not demonstrate efficacy.

Integrated Assessment of Effectiveness

The investigational drug product, BOTOX, did not demonstrate efficacy during Study 191622-137.

8.2. Review of Safety

Safety Review Approach

The safety review was based on data from Study 191622-137. The safety population includes all patients who received the study drug. Safety analyses are based on the actual treatment received. The reviewer focused primarily on data obtained during the 12 weeks following the first injection of study drug in Study 191622-137. Additional data from the study were reviewed for deaths and any safety signals identified.

Supportive sources of safety data included the extensive safety profile of BOTOX that has been characterized for other indications since its initial approval in 1989.

The following safety issues required particular attention in the safety evaluation because they are known concerns with BOTOX:

- Urinary tract infection
- Urinary retention
- Increased Residual Urine Volume
- Possible Distant Spread of Toxin
- Immunogenicity

8.2.1. Review of the Safety Database

Overall Exposure

The safety population is comprised of the 55 patients who underwent the treatment procedure

and received study drug on randomization/Day 1. Safety analyses were based on actual treatment received. If a patient received a different dose from the dose to which they were randomized (for example, dosing error), the patient was reassigned to the dose group of the actual dose received. Of the 55 patients who received at least one dose, 54 received treatment dose on Day 1 as randomized, while 1 patient was randomized to 25 U but received 100 U BOTOX on Day 1, due to a dosing error.

Table 11 demonstrates the participant overall exposure by sequence of treatment group. Of the initial 55 patients, all received at least 1 treatment, 46 received at least 2 treatments, 22 received at least 3 treatments, and only 4 received 4 treatments.[22]

Table 11. Participant Overall Exposure by Sequence of Treatment Group Used for Analysis BOTOX-Treated Population

Treatment Group Sequence	Total (N=55) n (%)
BOTOX 25U	3 (5.5)
BOTOX 25U-BOTOX 50U	7 (12.7)
BOTOX 25U-BOTOX 100U [1]	1 (1.8)
BOTOX 25U-BOTOX 25U-BOTOX 25U	1 (1.8)
BOTOX 25U-BOTOX 50U-BOTOX 50U	3 (5.5)
BOTOX 25U-BOTOX 50U-BOTOX 100U	1 (1.8)
BOTOX 25U-BOTOX 100U-BOTOX 25U [2]	1 (1.8)
BOTOX 25U-BOTOX 50U-BOTOX 50U-BOTOX 50U	1 (1.8)
BOTOX 50U	3 (5.5)
BOTOX 50U-BOTOX 50U	1 (1.8)
BOTOX 50U-BOTOX 100U	3 (5.5)
BOTOX 50U-BOTOX 50U-BOTOX 50U	3 (5.5)
BOTOX 50U-BOTOX 50U-BOTOX 100U	1 (1.8)
BOTOX 50U-BOTOX 100U-BOTOX 100U	5 (9.1)
BOTOX 50U-BOTOX 100U-BOTOX 100U-BOTOX 100U	1 (1.8)
BOTOX 100U	3 (5.5)
BOTOX 100U-BOTOX 100U	12 (21.8)
BOTOX 100U-BOTOX 100U-BOTOX 100U	3 (5.5)
BOTOX 100U-BOTOX 100U-BOTOX 100U-BOTOX 100U	2 (3.6)

Source: Study 191622-137 Study Report, Table 14.1-3.4, page 103/1413.

As shown in Table 12, cumulatively, the duration of exposure was longest for the 100 U BOTOX dose group. The mean duration of exposure to the 25 U dose was 40.1 weeks; to the 50 U dose, 49.3 weeks; and to the 100 U dose, 76.2 weeks.[23]

[22] 191622-137 Study body, page 50/1413.

[23] Study 191622-137 Study Report, Table 14.3-1.2, page 389/1413.

Table 12. Cumulative Duration of Study Drug Exposure BOTOX-Treated Population

	BOTOX 25U (N=16)	BOTOX 50U (N=29)	BOTOX 100U (N=31)
Duration of Exposure (weeks)			
>= 2 weeks	16 (100.0%)	29 (100.0%)	31 (100.0%)
>= 6 weeks	16 (100.0%)	29 (100.0%)	31 (100.0%)
>= 12 weeks	16 (100.0%)	28 (96.6%)	31 (100.0%)
>= 18 weeks	11 (68.8%)	21 (72.4%)	31 (100.0%)
>= 24 weeks	9 (56.3%)	18 (62.1%)	29 (93.5%)
>= 30 weeks	8 (50.0%)	16 (55.2%)	27 (87.1%)
>= 36 weeks	7 (43.8%)	14 (48.3%)	27 (87.1%)
>= 42 weeks	5 (31.3%)	14 (48.3%)	25 (80.6%)
>= 48 weeks	4 (25.0%)	14 (48.3%)	23 (74.2%)
>= 54 weeks	3 (18.8%)	11 (37.9%)	23 (74.2%)
>= 60 weeks	3 (18.8%)	11 (37.9%)	22 (71.0%)
>= 66 weeks	3 (18.8%)	10 (34.5%)	20 (64.5%)
>= 72 weeks	3 (18.8%)	10 (34.5%)	19 (61.3%)
>= 78 weeks	3 (18.8%)	9 (31.0%)	18 (58.1%)
>= 84 weeks	3 (18.8%)	7 (24.1%)	16 (51.6%)
>= 90 weeks	3 (18.8%)	6 (20.7%)	14 (45.2%)
>= 96 weeks	2 (12.5%)	6 (20.7%)	12 (38.7%)
n	16	29	31
Mean (SD)	40.1 (30.25)	49.3 (34.71)	76.2 (30.84)
Median	28.9	33.0	85.0
Q1, Q3	(16.9, 49.3)	(17.9, 80.7)	(47.0, 100.9)

Source: Study 191622-137 Study Report, Table 14.3-1.2, page 389/1413.

BOTOX

The BOTOX safety database includes 557 adult patients with OAB with symptoms of urge incontinence, urgency, and frequency, who received 100 U BOTOX via intradetrusor injection in 2 clinical trials: Studies OAB-1 and OAB-2. Patients received 20 injections of study drug spaced approximately 1 cm apart into the detrusor muscle, and the study duration was 24 weeks.

It is also supported by a safety database of 227 patients who received 200 U of BOTOX and 223 patients who received 300 U of BOTOX for urinary incontinence due to detrusor overactivity associated with a neurologic condition in two clinical studies: NDO-1 and NDO-2.

In addition, the data from Study 191622-120, includes 113 patients ages 5 to 17 years old with urinary incontinence due to detrusor overactivity associated with a neurologic condition and using CIC received 50U, 100U, or 200 U BOTOX, not to exceed 6 Units/kg body weight.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Safety variables included adverse events, serious adverse events, physical examination, vital signs, laboratory tests (urinalysis, hematology, and clinical chemistry), renal function (estimate of the glomerular filtration rate [eGFR]), PVR urine volume, use of CIC, kidney and bladder ultrasound, immunogenicity testing, concomitant medications, concurrent procedures, and a urine pregnancy test for females who were post menarche.[24]

[24] Study 191622-137 Synopsis, page 5/6.

The safety database aligns with advice in interactions with the Division during protocol development.[25, 26] The safety assessments are considered adequate.

Issues Regarding Data Integrity and Submission Quality

The submission contains all required components of the eCTD. The overall quality and integrity of the application appears to be acceptable. Requests for additional information from the Applicant throughout the review process were addressed in a timely fashion.

The study experienced challenges with recruitment. As a result, after agreement with the Agency, the study was terminated prior to reaching the initial enrollment target of 108 patients.

Reviewer's Comment*: On November 7, 2022, an Information Request was sent to the Sponsor requesting the define.xml file for the SDTM data, since this was not included in the submission. This was received on November 9, 2022 and was found to be acceptable.*

On November 15, 2022, an Information Request was sent to the Sponsor requesting a revised annotated case report form that is consistent with the Study Data Technical Conformance Guide specifications. In addition, the Information Request requested a revised CSDRG.pdf document with functional hyperlinks. These revised documents were received on December 1, 2022 and were acceptable.

On November 17, 2022, an Information Request was sent to the Sponsor requesting that they provide a rationale for assuming the applicability of foreign data to the U.S. population/practice of medicine. A response was received on November 21, 2022 and was found to be acceptable.

On November 18, 2022, an Information Request was sent to the Sponsor asking for the location of the Case Report Forms listed in section 16.3 of the eCTD. A response was received on November 21, 2022 and was acceptable.

On November 22, 2022 an Information Request requesting Narratives for each subject for whom there were dosing errors and Narratives for each subject who reported the adverse event of urethral pain or abdominal pain was sent to the Sponsor. A response was received on December 8, 2022 and found to be acceptable.

Categorization of Adverse Events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 24.1) and described using the preferred term. The Applicant presented adverse events in two ways: events occurring within the entire Treatment Cycle (from the time

[25] Medical Officer Review of Required Pediatric Study Protocol, IND 012430, 7/19/2013.

[26] Correspondence, Advice/Information Request, IND 012340, 7/25/2013.

of Treatment injection to time of retreatment or exit from the study) and events occurring within the first 12 weeks after BOTOX administration. This approach captures the AE profile within a cycle (since cycle length may vary) and within a standardized time frame/exposure period in each cycle, respectively.

The Applicant captured by cycle:

- All TEAEs
- Study drug-related TEAEs
- Study injection related TEAEs
- All TESAEs
- TEAEs leading to discontinuation

The protocol-defined specific adverse events are as follows:

- UTI:
  - a positive urine culture result with a bacteriuria count of > 10^5 CFU/mL, AND leukocyturia of > 5/hpf
- Urinary Retention:
  - PVR of ≥ 350 mL (regardless of symptoms), OR
  - PVR ≥ 200 mL and < 350 mL and the patient reports associated symptoms i.e., sensation of bladder fullness or inability to void despite persistent effort, that in the investigator's opinion require CIC.
- Increased Residual Urine Volume:
  - elevated PVR is clinically significant but does not fulfill the above definition for urinary retention.[27]

CDTL Comments: *UTI and urinary retention are reported adverse events in other BOTOX studies.*

Routine Clinical Tests

Routine clinical tests for safety included:

- Physical examination at screening and exit: general appearance, head, eyes, ears, nose, and throat, heart/cardiovascular, lungs, abdomen, neurologic, extremities, back, musculoskeletal, lymphatic, skin, genitourinary, and other findings.

[27] Study 191622-137, study protocol, section 9.1.2.

- Weight and height during the screening period, at the qualification for retreatment clinic visits if the patient qualifies, on each day of treatment prior to the injection procedure, and at the exit visit.
- Vital signs at each study clinic visit prior to any invasive procedures: pulse rate, blood pressure, respiration rate, and body temperature.
- Urinalysis, urine culture and sensitivity: urinalysis was performed at screening, and at all clinic visits. If there were findings suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as white blood cells, red blood cells, and/or bacteria), then urine culture and sensitivity were performed. Only central lab results were used in the statistical analysis.
- Hematology: A blood sample for hematology assays by a central laboratory were taken at the time the IV line was started for general anesthesia prior to each treatment administration (if no general anesthesia was administered a blood sample was taken prior to treatment). A blood sample was also taken at Week 12 after each treatment and at study exit.
- Clinical chemistry: A blood sample for nonfasting clinical chemistry assays by a central laboratory was taken at the time the IV line was started for general anesthesia prior to each treatment administration (if no general anesthesia was administered a blood sample was taken prior to treatment). A blood sample was also taken at Week 12 after each treatment and at study exit. Analytes Included the following (except at Week 12 where only blood urea nitrogen and creatinine were obtained): glucose, creatinine, blood urea nitrogen, total bilirubin, aspartate aminotransferase/ serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, alkaline phosphatase, uric acid, sodium, potassium, bicarbonate (carbon dioxide content chloride, phosphorus, calcium, magnesium, and total protein.
- Renal function testing: estimate of the glomerular filtration rate (eGFR); on the day of each treatment (prior to treatment), Week 12 after each treatment, and at study exit.
- Immunogenicity testing: collected prior to each treatment administration, at Week 12 after treatment 1, and at study exit.
- Kidney and bladder ultrasound during the screening period (which for this evaluation could include prior to randomization on day 1), at the qualification for retreatment clinic visit, and at the exit visit.
- Urine pregnancy test during the screening period for females who were post menarche prior to each treatment administration, at Week 12 after each treatment, and at exit. [28]

[28] Study 191622-137 Protocol, page 54/284.

8.2.3. Safety Results

Deaths

No deaths were reported during this study.

Serious Adverse Events

Treatment-emergent serious adverse events (TESAEs) were reported in Study 191622-137 in Cycle 1 in 1/55 (1.8 %) of patients. In Cycle 2, 1/46 (2.2 %) of patients were reported to have a TESAE. In Cycle 3, 1/22 (4.5 %) of patients were reported to have a TESAE. Overall, there were three patients, as described below, who reported six serious TEAEs including: abdominal pain, back pain, social problem, anxiety disorder, malaise, and pallor. None of the serious TEAEs were considered study treatment related by the investigator.[29]

Patient (b) (6): On Day 199 of treatment Cycle 2, a 16-year-old female in the 100 U BOTOX dose group experienced anxiety disorder. The event resolved by Day 213 and was considered severe and not related to study medication.

Patient (b) (6): A 15-year-old female in the 100 U BOTOX dose group experienced malaise and pallor on Day 13 of treatment Cycle 3. The events resolved by Day 17 and were considered moderate in severity and not related to study medication.

Patient (b) (6): On Study Day 34 during Treatment Cycle 1, a 17-year-old female patient in the 25 U dose group experienced TESAEs of abdominal pain, back pain, and social problem. All events were considered severe; the events of abdominal pain and back pain resolved on Study Day 315, and the event of social problem resolved on Study Day 50.

Reviewer's Comment: *This reviewer reviewed the narratives and concurs with the clinical judgement of the investigator.*

CDTL Comment: *Concur with clinical reviewer's conclusion.*

Dropouts and/or Discontinuations Due to Adverse Effects

Subject (Patient (b) (6)), a 12-year–old female with a history of OAB and ADHD, discontinued from Study 191622-137 due to a TEAE of vesicoureteral reflux. The patient received 50 U BOTOX during Treatment Cycle 1 on (b) (6) and was subsequently diagnosed with a mild UTI on (b) (6), that resolved on (b) (6) She received 100 U BOTOX during Treatment Cycle 2 on (b) (6) and was subsequently diagnosed with vesicoureteral reflux on (b) (6)

[29] Study 191622-137 Study Report body, page 79/1413.

that was moderate in severity. She discontinued from the study on (b) (6). The event was not considered related to the study drug.[30]

***Reviewer's Comment**: This event is unlikely to be related to the study drug due to the time course, but causality cannot definitively be ruled out.*

Significant Adverse Events

See Section 8.2.4. for significant adverse events which are submission-specific issues.

Treatment-Emergent Adverse Events and Adverse Reactions

In Study 191622-137, during the overall treatment Cycle 1, 72.2% (13/18) of patients in the 25 U, 70.6% (12/17) in the 50 U, and 70.0% (14/20) in the 100 U BOTOX dose group experienced 1 or more TEAEs. Most of the events were mild (43.6%, 24/55) or moderate (20.0%, 11/55) in severity. 7.3% (4/55) subjects experienced TEAEs that were considered related to study drug.[31] The most reported TEAEs during the first 12 weeks of treatment during Cycle 1 were nasopharyngitis (9.1%), dysuria (7.3%), urinary tract infection (5.5%), and abdominal pain (5.5%). Most of the treatment related TEAEs were considered related to study drug injection.

[30] Study 191622-137 Study Report body, page 73/1413

[31] 191622-137, Clinical Study Report, page 76/1413.

Table 13. TEAEs Observed ≥ 3% in All BOTOX Treatment Group: Patients in Descending Incidence Observed Up to Week 12 of Cycle 1 (BOTOX-Treated Population)

Preferred Term	BOTOX 25 U (n = 18) n (%)	BOTOX 50 U (n = 17) n (%)	BOTOX 100 U (n = 20) n (%)	All BOTOX (N=55) n (%)
Any Term	11 (61.1)	8 (47.1)	10 (50.0)	29 (52.7)
Nasopharyngitis	1 (5.6)	2 (11.8)	2 (10.0)	5 (9.1)
Dysuria	2 (11.1)	0 (0.0)	2 (10.0)	4 (7.3)
Urinary tract infection	2 (11.1)	0 (0.0)	1 (5.0)	3 (5.5)
Abdominal pain	2 (11.1)	1 (5.9)	0 (0.0)	3 (5.5)
Urethral pain	0 (0.0)	0 (0.0)	2 (10.0)	2 (3.6)
Abdominal pain lower	0 (0.0)	1 (5.9)	1 (5.0)	2 (3.6)
Headache	0 (0.0)	1 (5.9)	1 (5.0)	2 (3.6)
Urticaria	1 (5.6)	0 (0.0)	1 (5.0)	2 (3.6)
Tonsillitis	0 (0.0)	2 (11.8)	0 (0.0)	2 (3.6)
Nasal congestion	2 (11.1)	0 (0.0)	0 (0.0)	2 (3.6)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; Week 12 = Day 84.

Note: All treatment-emergent adverse events (TEAEs) are presented, regardless of relationship to treatment.

AE terms are coded using the dictionary: MedDRA Version 24.1.

Preferred terms are sorted by descending frequencies of treatment groups from right to left.

Within each preferred term, a patient is counted at most once.

Female = event specific to female; percentages for sex-specific TEAE are relative to the number of participants of the appropriate sex.

Cross-reference: Table 14.3-5.1

Source: Study 191622-137 Clinical Study Report, Table 13, Page 76/1413.

During treatment Cycle 2, 22/46 subjects experienced TEAEs. During treatment Cycles 3 and 4, 10/22 and 2/4 subjects experienced TEAEs, respectively. Most events were mild or moderate and did not require any medical intervention.[32]

The Applicant did not identify any dose-dependent relationship for TEAEs among the three treatment groups.

Dysuria was the most reported TEAE assessed by the investigator as related to the study injection procedure. Dysuria was reported in 4/55 (7.3%) of patients overall through Week 12 of Treatment Cycle 1.[33] During complete Treatment Cycle 1, 9.1% of BOTOX treated patients

[32] ibid, page 77/1413.

[33] Study 191622-137, Summary of Clinical Safety, page 13/31.

experienced dysuria. During Complete Treatment Cycle 2, 13% of patients experienced dysuria.

Other significant adverse events were identified by the Sponsor as UTI, urinary retention, residual urine volume, and PDSOT. These are reviewed in Section 8.5.

Abdominal Pain

Abdominal pain was reported by 3/55 (5.5%) of all BOTOX-treated patients through Week 12 of Treatment Cycle 1. In addition, lower abdominal pain was reported by 2/55 (3.6%) of BOTOX-treated patients through Week 12 of Treatment Cycle 1.[34] During the Complete Treatment Cycle 1, abdominal pain was reported by 7.3% of patients.[35]

Reviewer's Comment: *Narratives of patients who experienced mild to moderate abdominal pain immediately after the procedure and days after the treatment with the drug were reviewed at greater length. The mild local pain occurring postoperatively on the treatment day is most likely related to the study drug administration, however, it was mild and resolved on the same day. The generalized abdominal pain that occurred days later, does not appear to be temporally related to the study drug administration.*

Narratives for urethral pain were also reviewed by this clinical reviewer. The mild urethral pain occurring postoperatively on the treatment day is not unexpected and most likely may be related to the study drug administration, however, it was mild and resolved on the same day for most of the cases reviewed and did not require any further medical intervention.

CDTL Comment: *Agree with the clinical reviewer's judgement.*

Laboratory Findings

There were no observed clinically relevant changes from study baseline at Week 12 of treatment Cycle 1 in mean laboratory values for hematology and clinical chemistry variables.

Vital Signs

Blood Pressure

The Applicant did not report any subjects with a serious adverse event (SAE) of persistent hypertension or hypotension.

Clinical Reviewer's Comment: *This reviewer reviewed the instances of elevated blood pressure and instances of low blood pressure. There were two subjects with elevated blood pressure that*

[34] Study 191622-137, Summary of Clinical Safety, page 13/31.

[35] Study 191622-137, Summary of Clinical Safety, page 13/31.

were transient in nature. In one subject, the elevated blood pressure may have been procedure-related and did not need medical intervention. There were a couple of instances of hypotension that were sporadic and did not require medical intervention. Therefore, any changes in the blood pressure do not appear to be related to the study drug. The clinical reviewer does not have a concern for an association of hypertension or hypotension with BOTOX.

CDTL Comment: *Concur with the clinical reviewer's judgement.*

Pulse and Respiratory Rate

The Applicant reported that there were no clinically significant changes in vital signs related to safety during the study.

Clinical Reviewer's Comment*: This reviewer examined clinical changes in pulse and respiratory rate. In the reviewer's judgement, they do not appear to be related to the study drug.*

Electrocardiograms

Not done during the trial.

Immunogenicity

See Clinical Pharmacology review, Section 6.3.1.

8.2.4. Analysis of Submission-Specific Safety Issues

Safety issues that are specific to intradetrusor injection of BOTOX include UTI, urinary retention, residual urine volume, PDSOT, and immunogenicity. Each of these safety concerns and their frequency in Study 191622-137 is described below, except for immunogenicity, which is described above in Section 6.3.1.

Urinary Tract Infection

An adverse event of UTI was defined as a positive urine culture result with a bacteriuria count of > 10^5 CFU/mL plus leukocyturia of > 5/hpf. If a patient met the criteria for the definition of a UTI, the investigator recorded whether the UTI was "symptomatic" or "asymptomatic" on the adverse event eCRF.[36] If urinalysis/culture results were reported which, in the opinion of the investigator, were considered clinically significant but did not fulfill the above definition of a UTI, the findings were recorded as adverse events (e.g., bacteriuria, leukocyturia). A urine sample for urinalysis by a central laboratory was collected at all clinic visits. A urine culture and sensitivity test was performed when central laboratory urine results were suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as white blood

[36] Study 191622-137 Protocol, Section 9.1.2.

cells, red blood cells, and/or bacteria).[37] Assessments for UTI were done at Week 2, 6, and 12 post injection, and at subsequent clinic visits.[38] One TEAE of UTI was considered severe in subject (b) (6) and that subsequently resolved. None of the UTIs were considered as serious adverse events.

- Few UTIs occurred within the first 2 weeks after each treatment cycle; the incidence across all BOTOX groups in Cycle 1, 2, and 3 was 0% (0/55), 4.3.% (2/46) and 0% (0/22), respectively. Both events occurred during Treatment Cycle 2 in the 100 U dose group.
- Within the first 12 weeks after each treatment Cycle 1, 2, and 3, UTI was reported across all BOTOX groups in 5.5% (3/55), 23.9% (11/46) and 18.2% (4/22), respectively.
- During the full treatment Cycle 1, 2, and 3, urinary tract infection was reported across all BOTOX groups in 10.9% (6/55), 28.3% (13/46) and 27.3% (6/22), respectively.
- No UTI was reported during treatment Cycle 4.

UTIs were observed at a lower rate in patients during the Treatment Cycle 1 compared to Treatment Cycle 2 or Treatment Cycle 3. However, due to the small number of patients in each treatment cycle, one cannot draw inferences regarding any increased risk with repeated treatment.[39]

Table 14. Treatment-Emergent UTI Events Within First 12 Weeks After Treatment (BOTOX-Treated Population)

	BOTOX 25 U n (%)	BOTOX 50 U n (%)	BOTOX 100 U n (%)	All BOTOX n (%)
Treatment Cycle 1	2/18 (11.1)	0/17 (0.0)	1/20 (5.0)	3/55 (5.5)
Treatment Cycle 2	0/1 (0.0)	4/17 (23.5)	7/28 (25.0)	11/46 (23.9)
Treatment Cycle 3	0/2 (0.0)	1/7 (14.3)	3/13 (23.1)	4/22 (18.2)

BOTOX = Botulinum Toxin Type A; UTI = urinary tract infection

Note: The following 2 MedDRA terms were used to identify events of UTI: "urinary tract infection" and "urinary tract infection bacterial."

Cross-reference: Study 191622-137 CSR, Table 14.3-22.1

Source: Summary of Clinical Safety, Study 191622-137, Table 5.

[37] Study 191622-137 Protocol, Section 6.3.13

[38] Study 191622-137 Protocol, Table 1.

[39] Summary of Clinical Safety, Study 191622-137, page 16/31.

Table 15. Number (%) of Participants With Treatment-Emergent UTI During Entire Cycle

Study Treatment Cycle	BOTOX 25 U n/N (%)	BOTOX 50 U n/N (%)	BOTOX 100 U n/N (%)	Total n/N (%)
Cycle 1	2/18 (11.1)	2/17 (11.8)	2/20 (10.0)	6/55 (10.9)
Cycle 2	0/ 1 (0.0)	4/17 (23.5)	9/28 (32.1)	13/46 (28.3)
Cycle 3	0/ 2 (0.0)	2/ 7 (28.6)	4/13 (30.8)	6/22 (27.3)
Cycle 4	0/ 0	0/ 1 (0.0)	0/ 3 (0.0)	0/ 4 (0.0)

Source: Reviewer designed table, source: Table 14.3-22.1, Study 19622-137 Study Report, page 1223/1413
Abbreviations: UTI, urinary tract infection

Clinical Reviewer's Comment*: There is no discernable pattern of UTI incidence among different dose groups. The incidence of UTI was greater during repeat cycles of treatment, but groups are very small and therefore it is challenging to draw causal inferences. None of the UTIs were considered serious adverse events.*

Urinary Retention

Urinary retention was defined as an increased post void residual that required intervention with CIC with the following clinical findings: a PVR of ≥ 350 mL (regardless of symptoms), or PVR ≥ 200 mL and < 350 mL and the patient reported associated symptoms such as the sensation of bladder fullness or inability to void despite persistent effort, that in the investigator's opinion, required CIC.[40] The Applicant reported that one patient experienced urinary retention in treatment Cycle 2.

Patient (b) (6): 14-year-old female with a history of nocturnal enuresis, daytime incontinence, and dysfunctional voiding pattern. The patient who reported 2 urinary retention events was in the 100 U dose group. The event was reported 167 days after treatment Cycle 2. The PVR measurements were 0, 30, and 0 at the Week 2, 6 and 12 visits, respectively. Then, on Day 170, the PVR was measured at 300 ml and subsequently on Day 175 the PVR measured 0 ml. On Day 188, the PVR measurement was 357 mL, and the subject was started on CIC.

Reviewer's Comment: *The adverse event of urinary retention occurred 167 days after treatment, in a timeframe that was remote from the administration of BOTOX. Therefore, this event is not likely related to BOTOX administration.*

Residual Urine Volume

An adverse event of increased residual urine volume was defined as a raised PVR that was clinically significant in the investigator's opinion but did not fulfill the definition of urinary

[40] Study 191622-137, Study report, page 82/1413.

retention.[41] One patient in the 100 U BOTOX dose group reported residual urine volume on Day 29 after treatment Cycle 4, that was categorized as a TEAE.

Patient (b) (6): 15-year-old female with a history of duplex kidney. On (b) (6) BOTOX 100 U was administered per protocol in Study 191622-137. On (b) (6), the patient felt unwell, went to the emergency department, was admitted. Observation, urine dipstick and blood work were all found to be normal, however, ultrasound scan showed enlarged kidney. At a follow-up on (b) (6), it was reported that the events were fully resolved on (b) (6) There was an SAE of pallor, and the Investigator's and Sponsor's assessment was that this was not related to the study drug. Subsequently, the patient was reported to have a residual urine volume on Day 29 after treatment Cycle 4, that was categorized as a TEAE.

Post void residual volumes over 100 ml not categorized as TEAEs included the following:

- During treatment Cycle 1, one patient at Week 2 had a measurement of > 100 ml to < 200 ml.
- During treatment Cycle 2, 1 patient at Week 24 had a measurement of ≥ 200 ml and < 350 ml.
- During treatment Cycle 3, 2 patients at Week 48, 1 patient at Week 60, and 1 patient at Week 84 had a measurement of > 100 ml to < 200 ml.

Reviewer's Comment: *Increased residual urine volume is seen with BOTOX injections into the bladder wall.*

There was one patient who received 100 U BOTOX during Cycle 4 and was categorized as a TEAE for increased residual urine, but did not rise to the level of being diagnosed as urinary retention.

8.2.5. Possible Distant Spread of Toxin

PDSOT, a known adverse event associated with BOTOX, is defined as a possible pharmacologic effect of botulinum toxin at sites noncontiguous and distant from the site of injection.[42] BOTOX is injected directly into the urinary bladder for treatment of OAB, therefore, urinary retention is considered a localized effect of study drug, not a PDSOT. The MedDRA preferred terms evaluated for PDSOT included the following listed in Table 16.

[41] Study 191622-137 Study Report, page 82/1413.

[42] Study 191622-137, Summary of Clinical Safety, page 20/31

Table 16. MedDRA PTs Evaluated for Potential Distant Spread of Toxin

Cardiac disorders	**Nervous System Disorders**	**Respiratory, Thoracic and Mediastinal Disorders**
Bradycardia	Bell's palsy	Aspiration
Eye Disorders	Bulbar palsy	Diaphragmatic paralysis
Accommodation disorder	Cranial nerve palsies multiple	Dysphonia
Diplopia	Cranial nerve paralysis	Dyspnoea
Extraocular muscle paresis	Dysarthria	Pneumonia aspiration
Eyelid function disorder	Facial paralysis	Respiratory arrest
Eyelid ptosis	Facial paresis	Respiratory depression
Pupillary reflex impaired	Hyporeflexia	Respiratory failure
Vision blurred	Hypotonia	**Reproductive System and Breast Disorders**
Gastrointestinal Disorders	Paralysis	Pelvic floor muscle weakness
Constipation	Paresis cranial nerve	
Dry mouth	Peripheral nerve palsy	
Dysphagia	Peripheral paralysis	
Ileus paralytic	Speech disorder	
Infections and Infestations	Vocal cord paralysis	
Botulism	Vocal cord paresis	
Musculoskeletal and Connective Tissue Disorders	**Renal and Urinary Disorders**	
Muscular weakness	Urinary retention	

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

Source: Study 191622-137, Summary of Clinical Safety, page 21/31, Table 6.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term

There were four patients who experienced five TEAE events in Study 191622-137 that could be associated with PDSOT. The abbreviated narratives were reviewed by this clinical reviewer.

Reviewer's comment: *BOTOX is injected directly into the urinary bladder for treatment of OAB, therefore, urinary retention is considered a localized effect of study drug, not a PDSOT. In addition, there was no close temporal relationship between the events and the study drug administration supporting PDSOT. Some of events were confounded by anesthesia.*

Therefore, this reviewer agrees that the adverse event narratives do not support a mechanism of distant spread of toxin (DSOT).

CDTL Comment: *Concur with clinical reviewer's judgement.*

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

No COA analyses were done for safety.

Safety Analyses by Demographic Subgroups

The Applicant completed subgroup analyses up to Week 12 of Treatment Cycle 1 for sex, race, and region. Although there were some differences in AE frequencies across subgroups, there

was no consistent pattern. Study 191622-137 enrolled pediatric patients between the ages of 12 to 17 years, therefore the Applicant did not perform analyses of TEAEs by age subgroup.[43]

- Sex (female versus male): overall rates 53.2% (25/47) versus 50.0% (4/8). Dysuria, nasopharyngitis, and UTI were the most common TEAEs for female patients; urethral pain was the most common TEAE for male patients.
- Race (White versus non-White): No meaningful conclusion could be drawn since there were only 14 non-white patients, compared with 41 white patients.
- Region (North America versus other regions): 46.7% (7/15) versus 55.0% (22/40). Due to the small sample size for North America, a meaningful comparison could not be made for TEAEs among regions.

Reviewer's Comment: *The comparisons are difficult to interpret due to the low numbers of patients in some subgroups. Overall, the TEAEs related to BOTOX treatment experienced by patients aged 12 to 17 years with OAB in this study are consistent with those that have been reported in the adult OAB population.*

8.2.7. Specific Safety Studies/Clinical Trials

There were no additional safety studies or clinical trials in this submission.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The carcinogenic potential of BOTOX has not been evaluated.

Human Reproduction and Pregnancy

No pregnancies were reported during the study.[44]

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This drug has no abuse or dependence potential since it is physician-administered at intervals >12 weeks apart. The drug is not physically addictive.

[43] Study 191622-134, Summary of Clinical Safety, page 26/31.

[44] Study 191622-137 Study Report, page 88/1413.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant reported on the postmarketing experience with BOTOX.[45] The postmarketing database was queried for reports in pediatric patients received between January 1, 1990, and May 31, 2022, in which BOTOX was used for the following indications: bladder disorder, hypertonic bladder, incontinence, urinary incontinence, micturition urgency, micturition disorder, urge incontinence, and pollakiuria. There were 42 reports, containing 90 events, representing pediatric patients treated for pediatric OAB. The most frequent AE preferred terms were off label use (34), UTI (18), drug ineffective for unapproved indication (7), overdose (7), urinary retention (6), urinary incontinence (4), and drug ineffective (2).

There were five serious AEs, four of which were urinary retention, and one of which was a UTI. Of the four SAEs of urinary retention, three were medically confirmed and one was a consumer report. These reports originated from two literature articles and one spontaneous report received from a regulatory authority. The age of the patients varied between 1 and 18 years old, two of the patients were female, and in two cases the gender was unknown. The reported dose ranged between 100 U and 10 U/kg. Two of the patients were catheterized.[46]

Reviewer's Comment: *Urinary retention is a known localized pharmacological effect of BOTOX when it is injected into the bladder for adult OAB. In addition, urinary tract infection is a listed event when BOTOX is injected into the bladder for adult OAB.*

The Applicant did not have any ongoing or newly initiated clinical trials in the pediatric overactive bladder population and has not gathered or learned of any new safety data.

Clinical Reviewer's Comment: *The Applicant does not have any ongoing or newly initiated clinical trials in the pediatric overactive bladder population. The Applicant has not gathered or learned of any new safety data.*

Expectations on Safety in the Postmarket Setting

The Applicant is not seeking an approved indication for BOTOX for the treatment of pediatric overactive bladder. If the product is used off-label, based on the safety data presented in the application as well as that from the Applicant's postmarket databases and the literature, expectations in the postmarket setting of BOTOX in the pediatric OAB population reasonably include AEs of UTI, urinary retention, and increased urine residual volume.

[45] Study 191622-137 Summary of Clinical Safety, page 28/31.

[46] Study 191622-137 Summary of Clinical Safety, page 30/31.

8.2.10. Integrated Assessment of Safety

Consistent with the Division's guidance, the submission did not include an Integrated Summary of Safety.

Reviewer's Comment: *In the Written Responses dated 8/23/22 for IND 012430, the Division agreed that an Integrated Summary of Safety would not be required.*

8.3. Statistical Issues

No issues.

8.4. Conclusions and Recommendations

Study 191622-137 was undertaken by the Applicant to address a PREA requirement accompanying the approval of BOTOX for adult OAB. The study initially planned to enroll 108 children ages 12 to 17 years with OAB. However, in 2021, the Applicant requested a meeting with the Agency to gain input on their proposal to end the study prior to full enrollment and fulfill PREA. In consultation with the Division of Pediatric and Maternal Health (DPMH), DUOG recommended that the Sponsor stop further recruitment in Study 191622-137 and submit the data to date in a Labeling Supplement.

Study 191622-137 was conducted to evaluate the efficacy and safety of BOTOX in pediatric patients aged 12 to 17 years with overactive bladder. There was not a statistically significant difference in the mean change from baseline in the daily average frequency of daytime urinary incontinence episodes (primary efficacy endpoint) at Week 12 post-treatment. The adverse reactions in pediatric patients treated with BOTOX were comparable with the known safety profile in adults with overactive bladder. Therefore, the safety and effectiveness of BOTOX for the treatment of overactive bladder have not been established in pediatric patients. The benefit-risk balance for the 50 U BOTOX or 100 U BOTOX doses compared to 25 U BOTOX dose (the comparator group) was not favorable due to the lack of demonstrated efficacy and the known safety profile. We conclude that neither BOTOX 50 U nor BOTOX 100 U is an effective second line treatment in children 12 to 17 years of age with OAB who have not been adequately managed with anticholinergic therapy.

We recommend approval of SE-8, Labeling Supplement for changes to Section 8.4 of the PI for informational purposes regarding the results of Study 191622-137.

9 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting required and no external consultations for this application were sought.

10 Pediatrics

Study 191622-137 was undertaken by the Applicant to address a PREA requirement accompanying the approval of BOTOX for adult OAB. The study was conducted in children ages 12 years to 17 years with OAB. In consultation with the DPMH, the Division concluded that the Sponsor had fulfilled PREA requirement but not demonstrated efficacy in their study. The recommended labeling changes (seen below under Section 11.1) were made to the PI in consultation with DPMH.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted a supplement for BOTOX (onabotulinumtoxinA) for intradetrusor injection to add pediatric OAB safety and efficacy data to Section 8.4 (Pediatric Use) of the BOTOX PI and medication guide (MG) labeling. There will be no additional indications added to the label.

The Division of Medication Error Prevention and Analysis 2 (DMEPA 2) reviewed the proposed revisions to the BOTOX PI and MG. DMEPA did not identify any areas of vulnerability that may lead to medication errors. Additionally, DMEPA determined that the proposed revisions to Section 8.4 (Pediatric Use) of the PI and the language added to the MG do not necessitate revisions to Sections 2 (DOSAGE AND ADMINISTRATION), 3 (DOSAGE FORMS AND STRENGTHS), 16 (HOW SUPPLIED/STORAGE AND HANDLING), or 17 (PATIENT COUNSELING INFORMATION) of the PI nor to the container label or carton labeling. Therefore, DMEPA did not have specific recommendations at this time.

The submitted proposed draft label complies with the basic requirements of the Physician Labeling Rule and includes the following clinically relevant sections:

- Indications and Usage
- Dosage and Administration
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Clinical Studies

The following changes were made to Section 8.4 of the Label submitted.

Overactive Bladder

The safety and effectiveness of BOTOX for the treatment of overactive bladder have not been established in pediatric patients.

Efficacy was not demonstrated in a multicenter, randomized, double-blind, parallel-group, multiple-dose clinical study which was conducted to evaluate the efficacy and safety of BOTOX in pediatric patients aged 12 to 17 years with overactive bladder. Fifty-five patients who had an inadequate response to or were intolerant of at least one anticholinergic medication were treated with BOTOX. There was not a statistically significant difference in the mean change from baseline in the daily average frequency of daytime urinary incontinence episodes (primary efficacy endpoint) at Week 12 post-treatment when a medium and high dose were each compared to a low dose of BOTOX. The adverse reactions in pediatric patients treated with BOTOX were comparable with the known safety profile in adults with overactive bladder.

Other Prescription Drug Labeling

Minor edits were made to the Medication Guide as proposed by the Applicant.

12 Risk Evaluation and Mitigation Strategies

No risk evaluation and mitigation strategies are required for this application.

13 Postmarketing Requirements and Commitment

There will be no additional postmarketing requirements or commitments for this application.

14 Office Director (or Designated Signatory Authority) Comments

As signatory, I concur with the recommendation for approval of this Labeling Supplement. Study 191622-137 was required to fulfill PREA for pediatric OAB. The study did not demonstrate efficacy of Botox for pediatric OAB. The safety profile in the pediatric subjects is consistent with the known safety profile of the drug. I concur with the team's assessment that inclusion of this information in Section 8.4 of labeling is appropriate. Concurrence was obtained from PeRC and in further consultation with the oversight body, the PREA PMR is considered fulfilled.

15 Appendices

15.1. References

Literature

Austin, PF and S Abhishek, 2021, Functional Disorders of the Lower Urinary Tract in Children, Campbell-Walsh Urology, 12th Edition: Elsevier, 652-661.

Austin, PF, SB Bauer, W Bower, J Chase, I Franco, P Hoebeke, S Rittig, J Vande Walle, A von Gontard, A Wright, SS Yang, and T Neveus, 2014, The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society, J Urol, 191(6):1863-1865 e1813.

Austin, PF and GJ Vricella, 2015, Functional Disorders of the Lower Urinary Tract in Children, Campbell-Walsh Urology, 11th Edition: Elsevier, 3297-3316.

Chang, SJ, E Van Laecke, SB Bauer, A von Gontard, D Bagli, WF Bower, C Renson, A Kawauchi, and SS Yang, 2017, Treatment of daytime urinary incontinence: A standardization document from the International Children's Continence Society, Neurourol Urodyn, 36(1):43-50.

Mallinckrodt, CH, WS Clark, and SR David, 2001a, Accounting for dropout bias using mixed-effects models, J Biopharm Stat, 11(1-2):9-21.

Mallinckrodt, CH, WS Clark, and SR David, 2001b, Type I Error Rates from Mixed Effects Model Repeated Measures versus Fixed Effects Anova with Missing Values Imputed via Last Observation Carried Forward, Drug Information Journal 35:1215-1225.

Tekgul, S, R Stein, G Bogaert, S Undre, RJM Nijman, J Quaedackers, L t Hoen, R Kocvara, MS Silay, C Radmayr, and HS Dogan, 2020, EAU-ESPU guidelines recommendations for daytime lower urinary tract conditions in children, Eur J Pediatr, 179(7):1069-1077.

Other

Allergan, 1989, BOTOX prescribing information, accessed, 2023, https://www.rxabbvie.com/pdf/botox_pi.pdf.

15.2. Financial Disclosure

The Applicant/Sponsor submitted a Financial Certification and Disclosure (Section 1.3.4) for Study 191622-137. A list of investigators certifying the absence of financial interests and arrangements was submitted. The Applicant/Sponsor certified that (1) no financial arrangements with an investigator have been made where study outcome could affect

compensation; (2) the investigator does not have a proprietary interest in the tested product; (3) the investigator does not have a significant equity interest in the Sponsor; and (4) the investigator has not received significant payments of other sorts.

Table 17. Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Not applicable.

15.5. Additional Clinical Outcome Assessment Analyses

15.5.1. Additional Analyses

Table 18. Analysis of Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes LOCF Imputation Applied to Missing Values up to Week 12, Treatment Cycle 1 in Female Subjects Only for Study 137 (BOTOX-Treated Population).

Analysis Visit Statistics	BOTOX 25U (N=16)	BOTOX 50U (N=17)	BOTOX 100U (N=14)
Baseline			
Mean (SD)	5.67 (3.475)	3.54 (2.696)	4.09 (3.227)
Median	4.35	3.00	3.10
Q1, Q3	3.15, 6.20	2.20, 3.50	2.00, 5.40
Min, Max	2.4, 12.6	1.1, 12.6	0.4, 10.4
n	16	17	14
Week 12			
Mean (SD)	3.39 (4.045)	2.95 (4.470)	1.76 (1.748)
Median	2.40	1.40	1.10
Q1, Q3	0.90, 4.10	0.50, 2.90	0.40, 2.70
Min, Max	0.0, 15.7	0.0, 15.2	0.0, 5.2
n	16	17	14
Change from baseline			
Mean (SD)	-2.28 (3.687)	-0.58 (5.480)	-2.32 (1.987)
Median	-2.20	-1.30	-2.30
Q1, Q3	-4.05, -0.35	-2.10, -0.50	-3.60, -1.60
Min, Max	-10.0, 4.7	-12.6, 14.0	-5.4, 2.3
n [1]	16	17	14
95% CI [2]	(-4.246, -0.316)	(-3.400, 2.235)	(-3.469, -1.174)
P-value [2]	0.0258	0.6671	0.0008
Least square estimates [3]			
Mean (SE)	-1.47 (0.921)	-1.16 (0.883)	-2.54 (0.960)
95% CI	(-3.329, 0.386)	(-2.942, 0.618)	(-4.478, -0.608)
P-value	0.1175	0.1949	0.0112

Analysis Visit Statistics	BOTOX 25U (N=16)	BOTOX 50U (N=17)	BOTOX 100U (N=14)
vs. BOTOX 25U			
Difference (SE)		0.31 (1.301)	-1.07 (1.340)
95% CI		(-2.315, 2.934)	(-3.772, 1.630)
P-value		0.8131	0.4283

Source: Statistical Reviewer
[1] Number of subjects in the analysis;
[2] 95% CI and P-value from paired t-test of within-group mean change from baseline;
[3] Least square estimates and difference vs. control arm (BOTOX 25U) are based on ANCOVA model with baseline and treatment arm in the model.
Abbreviations: CI, confidence interval; LOCF, max, maximum; min, minimum; SD, standard deviation; SE, standard error

Table 19. Analysis of Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes LOCF Imputation Applied to Missing Values up to Week 12, Treatment Cycle 1 in Subjects Who Had Total of Baseline Daytime Urinary Urgency Incontinence Episodes Over the 2-Day Bladder Diary Collection Period Greater Than 6 Episodes for Study 137 (BOTOX-Treated Population)[4]

Analysis Visit Statistics	BOTOX 25U (N=8)	BOTOX 50U (N=5)	BOTOX 100U (N=4)
Baseline			
Mean (SD)	7.61 (3.996)	6.26 (3.744)	8.30 (2.149)
Median	6.20	5.20	8.70
Q1, Q3	4.20, 12.10	3.70, 6.40	6.75, 9.85
Min, Max	3.3, 12.6	3.4, 12.6	5.4, 10.4
n	8	5	4
Week 12			
Mean (SD)	4.55 (4.795)	3.36 (5.555)	3.80 (1.560)
Median	3.15	1.00	4.20
Q1, Q3	2.20, 5.00	0.00, 2.70	2.75, 4.85
Min, Max	0.0, 15.7	0.0, 13.1	1.6, 5.2
n	8	5	4
Change from baseline			
Mean (SD)	-3.06 (4.286)	-2.90 (7.430)	-4.50 (0.931)
Median	-3.50	-3.40	-4.50
Q1, Q3	-5.60, 0.05	-5.40, -1.00	-5.30, -3.70
Min, Max	-10.0, 3.6	-12.6, 7.9	-5.4, -3.6
n [1]	8	5	4
95% CI [2]	(-6.645, 0.520)	(-12.126, 6.326)	(-5.981, -3.019)
P-value [2]	0.0830	0.4321	0.0023
Least square estimates [3]			
Mean (SE)	-2.91 (1.617)	-3.64 (2.078)	-3.88 (2.306)
95% CI	(-6.400, 0.589)	(-8.133, 0.846)	(-8.867, 1.097)
P-value	0.0957	0.1031	0.1159
vs. BOTOX 25U			
Difference (SE)		-0.74 (2.645)	-0.98 (2.808)
95% CI		(-6.452, 4.976)	(-7.045, 5.086)
P-value		0.7845	0.7327

Source: Statistical Reviewer
[1] Number of subjects in the analysis;
[2] 95% CI and P-value from paired t-test of within-group mean change from baseline;
[3] Least square estimates and difference vs. control arm (BOTOX 25U) are based on ANCOVA model with baseline and treatment arm in the model.

[4] The baseline values of daytime urinary urgency incontinence episodes in 2-day collection period were used for the classification here, not the stratification value used for the randomization.
Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error.

Table 20. Analysis of Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes LOCF Imputation Applied to Missing Values up to Week 12, Treatment Cycle 1 in Subjects Who Had Total of Baseline Daytime Urinary Urgency Incontinence Episodes Over the 2-Day Bladder Diary Collection Period Less Than or Equal to 6 Episodes for Study 137 (BOTOX-Treated Population) [4]

Analysis Visit Statistics	BOTOX 25U (N=11)	BOTOX 50U (N=12)	BOTOX 100U (N=15)
Baseline			
Mean (SD)	3.28 (1.250)	2.40 (0.831)	2.53 (1.740)
Median	2.90	2.55	2.30
Q1, Q3	2.40, 4.20	1.70, 3.05	1.30, 3.90
Min, Max	1.7, 5.8	1.1, 3.5	0.4, 6.5
n	11	12	15
Week 12			
Mean (SD)	2.15 (2.575)	2.78 (4.211)	0.97 (1.161)
Median	1.90	1.45	0.50
Q1, Q3	0.40, 2.70	0.50, 2.90	0.00, 2.00
Min, Max	0.0, 9.2	0.0, 15.2	0.0, 3.7
n	11	12	15
Change from baseline			
Mean (SD)	-1.13 (2.782)	0.38 (4.489)	-1.56 (1.329)
Median	-1.00	-1.20	-1.70
Q1, Q3	-3.00, 0.90	-1.45, -0.35	-2.30, -0.90
Min, Max	-5.8, 4.7	-2.2, 14.0	-3.4, 2.3
n [1]	11	12	15
95% CI [2]	(-2.997, 0.742)	(-2.469, 3.235)	(-2.296, -0.824)
P-value [2]	0.2087	0.7729	0.0005
Least square estimates [3]			
Mean (SE)	-0.65 (0.886)	0.13 (0.833)	-1.71 (0.741)
95% CI	(-2.449, 1.154)	(-1.563, 1.822)	(-3.215, -0.202)
P-value	0.4699	0.8774	0.0275
vs. BOTOX 25U			
Difference (SE)		0.78 (1.234)	-1.06 (1.167)
95% CI		(-1.731, 3.286)	(-3.432, 1.310)
P-value		0.5331	0.3697

Source: Statistical Reviewer
[1]. Number of subjects in the analysis;
[2]. 95% CI and P-value from paired t-test of within-group mean change from baseline;
[3]. Least square estimates and difference vs. control arm (BOTOX 25U) are based on ANCOVA model with baseline and treatment arm in the model.
[4]. The baseline values of daytime urinary urgency incontinence episodes in 2-day collection period were used for the classification here, not the stratification value used for the randomization.
Abbreviations: CI, confidence interval; LOCF, last observation carried forward; SD, standard deviation; SE, standard error.

Table 21. Analysis of Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes LOCF Imputation Applied to Missing Values up to Week 12, Treatment Cycle 1 in White Subjects Only for Study 137 (BOTOX-Treated Population)

Analysis Visit Statistics	BOTOX 25U (N=13)	BOTOX 50U (N=12)	BOTOX 100U (N=16)
Baseline			
Mean (SD)	5.29 (4.121)	3.48 (3.107)	3.96 (3.122)
Median	3.30	2.80	2.55
Q1, Q3	2.90, 5.80	1.70, 3.55	1.70, 5.95
Min, Max	1.7, 12.6	1.1, 12.6	0.4, 10.4
n	13	12	16
Week 12			
Mean (SD)	3.04 (4.092)	3.44 (5.290)	1.68 (1.766)
Median	2.60	0.70	0.75
Q1, Q3	0.50, 2.80	0.00, 4.20	0.40, 3.20
Min, Max	0.0, 15.7	0.0, 15.2	0.0, 5.2
n	13	12	16
Change from baseline			
Mean (SD)	-2.25 (3.684)	-0.04 (6.412)	-2.28 (1.846)
Median	-1.40	-1.20	-2.10
Q1, Q3	-3.80, 0.10	-2.15, 1.20	-3.50, -1.50
Min, Max	-10.0, 3.6	-12.6, 14.0	-5.4, 2.3
n [1]	13	12	16
95% CI [2]	(-4.480, -0.028)	(-4.115, 4.032)	(-3.258, -1.292)
P-value [2]	0.0476	0.9824	0.0002
Least square estimates [3]			
Mean (SE)	-1.60 (1.025)	-0.51 (1.058)	-2.45 (0.911)
95% CI	(-3.678, 0.476)	(-2.657, 1.632)	(-4.298, -0.606)
P-value	0.1269	0.6310	0.0106
vs. BOTOX 25U			
Difference (SE)		1.09 (1.489)	-0.85 (1.378)
95% CI		(-1.929, 4.106)	(-3.643, 1.941)
P-value		0.4695	0.5405

Source: Statistical Reviewer
[1] Number of subjects in the analysis;
[2] 95% CI and P-value from paired t-test of within-group mean change from baseline;
[3] Least square estimates and difference vs. control arm (BOTOX 25U) are based on ANCOVA model with baseline and treatment arm in the model.
Abbreviations: CI, confidence interval; LOCF, last observation carried forward; SD, standard deviation; SE, standard error.

Table 22. Analysis of Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes up to Week 12, Treatment Cycle 1 Using Mixed-Effect Model Repeated Measures (MMRM) for Study 191622-137 (BOTOX-Treated Population)

Analysis Visit Statistics	BOTOX 25U (N=19)	BOTOX 50U (N=17)	BOTOX 100U (N=19)
Baseline			
Mean (SD)	5.11 (3.450)	3.54 (2.696)	3.74 (2.995)
Median	4.10	3.00	2.40
Q1, Q3	2.90, 6.10	2.20, 3.50	1.40, 5.40
Min, Max	1.7, 12.6	1.1, 12.6	0.4, 10.4
n	19	17	19

Analysis Visit Statistics	BOTOX 25U (N=19)	BOTOX 50U (N=17)	BOTOX 100U (N=19)
Week 2			
Mean (SD)	1.78 (2.376)	1.94 (2.790)	1.88 (2.779)
Median	0.90	1.00	0.85
Q1, Q3	0.00, 2.70	0.00, 3.30	0.00, 2.40
Min, Max	0.0, 8.7	0.0, 8.6	0.0, 8.7
n	18	15	18
Change from baseline			
Mean (SD)	-3.36 (2.591)	-1.67 (4.163)	-1.86 (2.058)
Median	-3.05	-1.40	-1.55
Q1, Q3	-4.20, -1.90	-2.50, -0.30	-2.30, -0.60
Min, Max	-9.9, 1.0	-12.6, 7.4	-8.0, 1.9
n [1]	18	15	18
95% CI [2]	(-4.649, -2.073)	(-3.979, 0.632)	(-2.879, -0.832)
P-value [2]	<0.0001	0.1418	0.0014
Least square estimates [3]			
Mean (SE)	-2.67 (0.553)	-2.01 (0.588)	-2.11 (0.547)
95% CI	(-3.776, -1.555)	(-3.186, -0.825)	(-3.203, -1.009)
P-value	<0.0001	0.0013	0.0003
vs. BOTOX 25U			
Difference (SE)		0.66 (0.815)	0.56 (0.783)
95% CI		(-0.976, 2.295)	(-1.013, 2.131)
P-value		0.4220	0.4785
Week 6			
Mean (SD)	2.59 (3.939)	1.65 (2.286)	2.13 (3.543)
Median	1.05	1.00	0.80
Q1, Q3	0.40, 3.20	0.00, 1.90	0.00, 2.10
Min, Max	0.0, 16.2	0.0, 7.7	0.0, 13.2
n	18	17	19
Change from baseline			
Mean (SD)	-2.62 (3.295)	-1.88 (3.562)	-1.61 (2.079)
Median	-2.95	-1.60	-1.60
Q1, Q3	-5.20, -1.20	-2.50, -1.10	-2.30, -0.60
Min, Max	-8.7, 4.1	-12.6, 4.8	-7.3, 2.8
n [1]	18	17	19
95% CI [2]	(-4.255, -0.978)	(-3.714, -0.051)	(-2.613, -0.608)
P-value [2]	0.0036	0.0446	0.0034
Least square estimates [3]			
Mean (SE)	-2.05 (0.657)	-2.21 (0.682)	-1.83 (0.644)
95% CI	(-3.367, -0.731)	(-3.577, -0.839)	(-3.122, -0.538)
P-value	0.0030	0.0021	0.0064
vs. BOTOX 25U			
Difference (SE)		-0.16 (0.953)	0.22 (0.924)
95% CI		(-2.073, 1.755)	(-1.636, 2.074)
P-value		0.8683	0.8134
Week 12			
Mean (SD)	3.16 (3.755)	2.95 (4.470)	1.56 (1.692)
Median	2.60	1.40	0.60
Q1, Q3	0.50, 3.40	0.50, 2.90	0.40, 2.70
Min, Max	0.0, 15.7	0.0, 15.2	0.0, 5.2
n	19	17	19

Analysis Visit Statistics	BOTOX 25U (N=19)	BOTOX 50U (N=17)	BOTOX 100U (N=19)
Change from baseline			
Mean (SD)	-1.94 (3.522)	-0.58 (5.480)	-2.18 (1.742)
Median	-1.40	-1.30	-2.00
Q1, Q3	-3.80, 0.10	-2.10, -0.50	-3.40, -1.40
Min, Max	-10.0, 4.7	-12.6, 14.0	-5.4, 2.3
n [1]	19	17	19
95% CI [2]	(-3.640, -0.244)	(-3.400, 2.235)	(-3.018, -1.339)
P-value [2]	0.0272	0.6671	<0.0001
Least square estimates [3]			
Mean (SE)	-1.46 (0.767)	-0.91 (0.807)	-2.40 (0.762)
95% CI	(-3.000, 0.078)	(-2.528, 0.712)	(-3.928, -0.868)
P-value	0.0624	0.2659	0.0028
vs. BOTOX 25U			
Difference (SE)		0.55 (1.119)	-0.94 (1.085)
95% CI		(-1.692, 2.799)	(-3.115, 1.241)
P-value		0.6231	0.3917

Source: Statistical Reviewer
[1]. Number of subjects in the analysis;
[2]. 95% CI and P-value from paired t-test of within-group mean change from baseline;
[3]. Least square estimates and difference vs. control arm (BOTOX 25U) are based on MMRM approach.
Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error

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/s/

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