NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	SE-1 Efficacy Supplement
Application Number(s)	sBLA 103000 / S-5318
Priority or Standard	Standard
Submit Date(s)	April 10, 2020
Received Date(s)	April 10, 2020
PDUFA Goal Date	February 10, 2021
Division/Office	Division of Urology, Obstetrics, and Gynecology/Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Review Completion Date	February 8, 2021
Established/Proper Name	Onobotulinumtoxin A
Trade Name	BOTOX
Pharmacologic Class	Acetylcholine release inhibitor
Code name	
Applicant	Allergan, Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	200 U of BOTOX per treatment not to exceed 6 U/kg body weight
Applicant Proposed Indication(s)/Population(s)	Treatment of (b) (4) detrusor overactivity (b) (4) in pediatric patients 5 (b) (4) who have an inadequate response to, are intolerant of, (b) (4) anticholinergic medication
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of neurogenic detrusor overactivity in pediatric patients 5 (b) (4) who have an inadequate response to or are intolerant of antimuscarinic antagonist medication
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	200 U of BOTOX per treatment in children ≥34 kilograms or 6 units/kg body weight in children <34 kilograms.

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Glossary

AE	adverse event
ANCOVA	analysis of covariance
ATP	adenosine triphosphate
AUC	area under the curve
BAB	binding antibody
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CIC	clean intermittent catheterization
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
CSR	clinical study report
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DBP	diastolic blood pressure
DHOT	Division of Hematology Oncology Toxicology
DLPP	detrusor leak point pressure
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRUP	Division of Reproductive and Urologic Products
DSOT	distant spread of toxin
DUOG	Division of Urology, Obstetrics, and Gynecology
eCTD	electronic common technical document
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	good clinical practice
GERD	gastrointestinal reflux disease
ICH	International Conference on Harmonisation
IDC	involuntary detrusor contraction
IND	Investigational New Drug
IV	intravenous
LOCF	last observation carried forward
LS	least squares
MCC	maximum cystometric capacity
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MPA	mouse protection assay
MS	multiple sclerosis
NAB	neutralizing antibody
NDA	new drug application
NDO	neurogenic detrusor overactivity

OSI	Office of Scientific Investigation
OAB	overactive bladder
PdetMax	maximum detrusor pressure
PDSOT	potential distant spread of toxin
PeRC	Pediatric Review Committee
PI	prescribing information
PinQ	Pediatric Incontinence Questionnaire
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SBP	systolic blood pressure
SCI	spinal cord injury
STEAE	serious treatment-emergent adverse event
TBS	Treatment Benefit Scale (modified)
TEAE	treatment-emergent adverse event
UTI	urinary tract infection
WBC	white blood cell

1. Executive Summary

1.1. Product Introduction

BOTOX is a sterile, vacuum-dried purified botulinum toxin type A. Botulinum toxin prevents muscular contraction by inhibiting release of acetylcholine at the neuromuscular junction. BOTOX was first approved in the U.S. in 1989 and is currently approved for several indications, including the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (NDO) [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication. The approval for the adult NDO 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

To address the PREA requirements accompanying the approval of BOTOX for adult NDO, BOTOX was studied in two clinical trials in 113 children ages 5 to 17 years with NDO. The first study, 191622-120, was a multicenter, randomized, double-blind, parallel group study evaluating the efficacy and safety of 3 doses (50 U, 100 U, 200U) in a single treatment cycle. This study assessed drug effect on clinical outcomes recorded in a patient urinary diary, including daytime urinary incontinence episodes (primary endpoint) and urine volume at first catheterization in the morning, and urodynamic measurements, including maximum detrusor pressure during the storage phase. This study provided the primary support of the efficacy of BOTOX. The second study, 191622-121, was a blinded, extension study evaluating the long-term efficacy and safety of BOTOX in patients treated in study 191622-120 who were eligible for retreatment for up to three additional treatments of BOTOX. The treatment doses administered (50 U, 100 U, or 200 U) were not randomized.

In study 192622-120, all 3 BOTOX dose groups (50 U, 100 U and 200 U) were able to, from baseline, similarly reduce the number of daytime urinary incontinence episodes, increase urine volume at first catheterization in the morning, and show an improvement in the urodynamic measurements of bladder capacity and maximum bladder pressure during the storage phase. However, the BOTOX 200 U dose group had the greatest proportion of patients achieving a reduction in maximum detrusor pressure below 40 cm H_20, a clinical threshold vital to preserving upper urinary tract function, including renal function. Findings from study 191622-121 demonstrated evidence of durability of effect with interpretable efficacy results maintained over three total treatment cycles. The safety profile of BOTOX for the treatment of NDO in children ages 5 to 17 years was acceptable and similar across the three dose groups evaluated. Safety appears stable with repeated treatments, though few patients had as many as four cycles. Adverse reactions including urinary tract infection (UTI), bacteriuria and hematuria were similar to the adult NDO program except for urinary retention which was not seen in the pediatric population because they all had clean intermittent catheterization (CIC). Specific to the pediatric NDO indication, these adverse reactions can be adequately managed by labeling.

Specific to BOTOX as a product, known labelled safety concerns remain for potential distant spread of toxin (PDSOT) and immunogenicity.

Comparing the benefit-risk balance for the 3 BOTOX doses, the 200U dose has the most favorable profile, given its dose-response benefit in lowering maximal detrusor pressure. We conclude that BOTOX 200 U is a safe and effective second line treatment for NDO in children ages 5 years and older who do not respond to or who cannot tolerate anticholinergic medications. Due to the 6U/kg weight cap stipulated in the two pediatric studies, children weighing <34 kg were not eligible for the 200 U dose and the same limit would hold true if only the 200U dose were to be approved. Therefore, post hoc exploratory safety and efficacy analyses were conducted for patients who weighed <34 kg and received <200 U in the studies. These analyses showed that the safety and efficacy were similar to that of the 200 U dose group. This is further supported by the evidence that the safety and efficacy of BOTOX were similar across the 50 U, 100 U, and 200 U dose groups. Therefore, for children <34 Kg in weight, BOTOX 6 U/Kg but with a total dose less than 200 U is safe and effective.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pediatric neurogenic detrusor overactivity (NDO) can be caused by a neurologic condition that impacts the brain, spinal cord, or peripheral nervous system and interrupts the signaling pathways controlling bladder function. In children, the most common cause is spina bifida, a group of developmental abnormalities that result from defects that occur during neural tube closure. The medical need for treatment is the highest in patients with NDO with detrusor sphincter dyssynergia. The involuntary detrusor contractions (IDCs) that occur during the bladder filling phase cause cyclical bladder pressure elevation which can in turn lead to vesicoureteral reflux and permanent renal injury including unilateral or bilateral hydronephrosis, hydroureteronephrosis and renal failure. These deleterious effects are seen on average by age three and can be seen as early as age 6 months. Treatment is aimed at reducing bladder pressures, achieving continence in school age children, minimizing urinary stasis and preserving the upper urinary tract over the long term. Because pediatric NDO is a condition with serious lifelong consequences for bladder and renal function, treatment is often initiated early in childhood. Currently, clean intermittent catheterization (CIC) is recommended for NDO children to ensure regular emptying of the bladder to prevent urinary stasis and increased bladder pressure, as well as to minimize incontinence. Current pharmacotherapy is limited to one drug class, anticholinergics, which are associated with several unpleasant or intolerable adverse reactions, including but not limited to: dry mouth, headache, intestinal symptoms such as constipation, dizziness and somnolence. There have also been reports of serious hypersensitivity reactions, including angioedema and anaphylaxis. Approximately 10% of NDO children either do not respond to or cannot tolerate anticholinergics (Verpoorten and Buyse 2008; Lehnert et al. 2012). If anticholinergic medications in combination with CIC are not effective or are not tolerated, bladder augmentation surgery may be necessary. Surgical interventions carry inherent risks, including but not limited to: postoperative ileus, transient urinary fistula, wound infection, bleeding requiring reoperation, thromboembolic complications, metabolic disturbances, ulceration or perforation of the bladder or its gastric segment, urinary stone formation, risk of malignancy, bowel disturbances and a need for repeat surgery. There is an unmet need for additional pharmacologic treatment for NDO children intolerant of or unresponsive to anticholinergic medications.

BOTOX is a sterile, vacuum-dried purified botulinum toxin type A. Botulinum toxin prevents muscular contraction by inhibiting release of acetylcholine at the neuromuscular junction. BOTOX was first approved in the U.S. in 1989 and is currently approved for several indications including the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication. The approval for the adult NDO indication included requirement for pediatric assessment, under the Pediatric Research Equity Act (PREA, 21 USC 355c). To

address these PREA requirements, BOTOX was studied in two clinical trials in 113 children ages 5-17 years with NDO. The first study, 191622-120, which provided the primary evidence of efficacy, was a multicenter, randomized, double-blind, parallel group study of three BOTOX dose groups (50 U, 100 U and 200 U) lasting a single treatment cycle (12 weeks). Patients were randomized in a 1:1:1 ratio of 50 U, 100 U, or 200 U BOTOX (not to exceed 6 U/kg). Randomization was stratified by age (<12 years or ≥12 years) and baseline daytime urinary incontinence episodes (a total of ≤6 episodes or >6 episodes over the 2-day bladder diary collection period).

The second study, 191622-121, was a multicenter, double-blind, long-term extension study where eligible patients from study 191622-120 could have up to three additional treatment cycles of BOTOX (50 U, 100 U, and 200 U, not to exceed 6U/kg).

BOTOX was administered via a surgical procedure: patients received anesthesia and pre-operative antibiotics. BOTOX was then administered via cystoscopy, with 20 injections of 0.5 mL each into the detrusor muscle avoiding the trigone area. Patients were followed with clinic visits at weeks 2, 6, and 12, and alternating telephone and clinic follow-up every 6 weeks until they exited the study. Patients exited the first study once they qualified for retreatment (after Week 12) or at week 48, whichever was earlier. Retreatment was based on patient request, and qualifications included: at least 12 weeks had elapsed since the previous BOTOX injection, at least two daytime urinary incontinence episodes over the 2-day diary collection period, and no serious adverse reaction at any time. Patients could request a higher dose with subsequent treatment cycles. The dose received during the retreatment was dependent on the assessment of the clinical response (efficacy and safety) to the previous blinded study treatment (50 U, 100 U, or 200 U BOTOX, not exceeding 6 U/kg). In the second study, although the doses were not randomized, investigators and patients remained blinded to the dose actually received upon retreatment. Patients are followed for 12 weeks after the last BOTOX injection.

BOTOX doses of 50 U, 100 U and 200 U were similarly effective in reducing from baseline the number of daytime urinary incontinence episodes at Week 6, the prespecified primary efficacy endpoint, and the magnitude was clinically significant. There was a dose-response in the reduction of the maximum detrusor pressure in storage phase; compared to the two lower dose groups, the BOTOX 200 U group had the greatest proportion of patients with an absolute reduction in maximum detrusor pressure below 40 cm H_20; this specific threshold is clinically significant as it is a urodynamic treatment goal aimed at preserving renal function. There was evidence of durability of effect. Although patients could request additional treatment after 12 weeks or more from the last injection, the median time to request for retreatment ranged from 24.1-29.6 weeks for the 3 dose groups. Efficacy as measured by clinical outcomes (e.g., urinary incontinence episodes, morning urine volume catheterized) was maintained over three treatment cycles. Efficacy appears to be maintained over the fourth treatment cycle also, however, there were too few patients for meaningful interpretation of those data. The safety profile of BOTOX was similar across the 3 dose groups and also similar to the adult NDO population, with the exception of urinary retention as children with NDO perform CIC. The most common adverse reactions included urinary tract infection (UTI), bacteriuria and hematuria. There was no dose-response in any adverse reactions. The safety

findings appear to be similar with repeated treatment, with no evidence of increased incidence in adverse reactions, though few patients had as many as four cycles.

The benefit-risk assessment supports approval of BOTOX 200 U over the lower doses. BOTOX 200 U reduced daytime urinary incontinence episodes and was most effective at reducing maximum detrusor pressure to below 40 cm H_2O. BOTOX 200 U also has an acceptable safety profile, with safety similar to the lower doses studied. For children who weigh less than 34 kg and would not be eligible to receive BOTOX 200 U, the benefit-risk assessment for the dose of 6U/kg supports approval. The efficacy was similar to that of the 200 U dose group. The safety profile of the 50 U, 100 U and 200 U doses was similar, and the additional safety analyses of patients who were reassigned to treatment groups based on the 6 U/kg weight cap, although based on a limited number of patients, did not reveal unexpected findings. Therefore safety for children treated with 6U/kg (but a total dose <200 U) is expected to be similar. BOTOX 200 U, (not to exceed 6 U/Kg) for children >34 Kg weight) is a safe and effective second line treatment for pediatric NDO in children ages 5-17. For children of <34 Kg weight, BOTOX dose 6 U/Kg body weight, is similarly efficacious and safe.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NDO can be caused by a neurologic condition that impacts the brain or spinal cord and interrupts the signaling pathways controlling bladder function. The most common cause is spina bifida, a congenital anomaly. • Detrusor overactivity is characterized by IDCs during the bladder filling phase. • IDCs cause cyclical bladder pressure elevation which can in turn lead to vesicoureteral reflux and permanent renal injury including unilateral or bilateral hydronephrosis, hydroureteronephrosis and renal failure. These deleterious effects are seen on average by age three and can be seen as early as age 6 months. • Children should be evaluated regularly with urodynamics/video-urodynamics and ultrasound. Treatment is aimed at reducing bladder pressure, minimizing urinary stasis and preserving the upper urinary tract.	Pediatric NDO is a condition with serious lifelong consequences for bladder and renal function. Injury to the upper urinary tract can occur in very young children and treatment is needed early on to preserve the renal function.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current treatment options include: – Clean intermittent catheterization, recommended for all patients – Anticholinergic/antimuscarinic agents approved for pediatric NDO. Only two treatments - oxybutynin (NDAs 017577, 018211 and 020897) and solifenacin (NDA 209529) – are currently approved for this use. – Other anticholinergic/antimuscarinic agents which are approved, but not for the indication of pediatric NDO: tolterodine (NDAs 020771 and 021228), fesoterodine (NDA 022030), darifenacin (NDA 021513) and trospium chloride (NDA 021595). – Anticholinergic agents frequently produce adverse reactions including dry mouth, headaches, intestinal symptoms such as constipation, dizziness and somnolence. Some anticholinergics result in adverse reactions such as angioedema or anaphylaxis. – 10% of pediatric NDO patients either do not respond to or cannot tolerate anticholinergic medications. – Bladder augmentation surgery, surgery to the bladder neck/outlet. These surgeries can be accompanied by serious early and late complications including but not limited to: postoperative ileus, transient urinary fistula, wound infection, bleeding requiring reoperation, thromboembolic complications, metabolic disturbances, ulceration or perforation of the bladder or its gastric segment, urinary stone formation, risk of malignancy, bowel disturbances and a need for repeat surgery	Current drug options are limited to one drug class, anticholinergics, which are associated with several unpleasant or intolerable adverse reactions. Approximately 10% of patients either do not respond to or cannot tolerate anticholinergics. Current treatment option for these children is surgery, which carries inherent risks, including potentially serious early and late complications. There is an unmet need for additional pharmacologic treatment in children intolerant of or unresponsive to anticholinergic medications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• BOTOX doses of 50 U, 100 U and 200 U were equally effective in reducing from baseline the number of daytime urinary incontinence episodes at Week 6, the prespecified primary endpoint. • There was a dose-response in the reduction of maximum detrusor pressure. The BOTOX 200 U group had the greatest proportion of patients who achieved an absolute reduction in maximum detrusor pressure below 40 cm H_20. • BOTOX doses of 50 U, 100 U and 200 U were similarly effective on other urodynamic measures. • The median time to request for retreatment ranged from 24.1-29.6 weeks for all 3 dose groups. Efficacy as measured by clinical outcomes was maintained over three treatment cycles. (Efficacy appears to be maintained over the fourth treatment cycle, but there were too few patients for meaningful interpretation of those data.) • Post hoc exploratory analyses of the efficacy of children who received less than the total dose of 200 U because of the maximum dosing limit of 6U/kg showed comparable reduction from baseline in the number of daytime urinary incontinence episodes to that of the 200 U dose, and also showed a reduction in maximum detrusor pressure and other urodynamic measures.	BOTOX is an effective second-line agent for pediatric NDO patients who do not respond to anticholinergic agents or who cannot tolerate them. Although the efficacy of the 3 dose groups (50U, 100 U, and 200 U) were similar in most of the clinical and urodynamic outcomes, the 200 U dose resulted in the greatest proportion of patients with a maximum detrusor pressure below 40 cm H20, a clinically significant treatment goal in preserving the upper urinary tract, including renal function.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• BOTOX requires a surgical procedure (cystoscopy): patients receive anesthesia and preprocedure antibiotics. BOTOX is then administered via cystoscopy, with 20 injections of 0.5 mL each into the detrusor muscle avoiding the trigone. • BOTOX for the treatment of pediatric NDO in children ages 5-17 years appears safe at the three doses studied, 50 U, 100 U and 200 U, and for the subgroup receiving 6U/kg based on the weight cap, with no apparent differences in the safety betweenamong these doses. There was no identifiable dose relationship for treatment-emergent adverse events (TEAEs) or any other safety concern among the three BOTOX treatment groups. There was also no identifiable change in the safety profile with repeated treatments (though there were fewer patients in the latter cycles). • The most commonly reported TEAEs were UTI and bacteriuria, as expected based on the underlying condition. • There were no differences in safety by subgroup (age, sex, race, etiology of NDO, region of the world, anesthesia or baseline anticholinergic use). • There was no evidence of distant spread of toxin (DSOT) in the clinical studies; potential distant spread of toxin (PDSOT) remains a boxed warning for the product. • There does not appear to be any impact of immunogenicity on safety.	The safety profile of BOTOX for the treatment of NDO in children ages 5-17 years was similar across the three doses studied, 50 U, 100 U and 200 U and for the subgroup receiving 6U/kg based on the weight cap, with no important differences in the type or incidence of adverse reactions. Safety appears stable with repeated treatments, though few patients had as many as four cycles. Specific to this indication, labeling is adequate to manage these adverse reactions.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X□	Clinical outcome assessment (COA) data, such as		
		X□	Patient-reported outcome (PRO)	Section 8.1.2
		□	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

Normal micturition involves passive, low-pressure filling of the bladder during the urine storage phase and coordination of detrusor contraction with internal and external urinary sphincter relaxation during voiding. Detrusor overactivity is a condition characterized by involuntary detrusor contractions (IDCs) during the bladder filling phase. Neurogenic detrusor overactivity (NDO) is detrusor overactivity caused by a neurologic condition that impacts the brain or spinal cord and interrupts the signaling pathways controlling bladder function. Spina bifida, a congenital anomaly characterized by the incomplete closure of membranes around the spine during embryonal development, is the most common cause of NDO in children. Urinary symptoms are present in more than 90% of these patients.

IDCs cause cyclical bladder pressure elevation and can cause fibrosis and decreased elasticity of the bladder wall. The increase in bladder pressure can lead to vesicoureteral reflux and permanent renal injury, including unilateral or bilateral hydronephrosis, hydroureteronephrosis and renal failure. According to a consult from the Division of Pediatric and Maternal Health, (See Section 10) evidence of renal injury, dilatation of the upper urinary tracts and urinary retention develop on average by age three in patients with congenital neural tube defects, and can be seen as early as age 6 months. Patients can also develop ureteric and kidney stones and recurrent urinary tract infections. Most patients have bacterial colonization of the urinary tract and abnormalities are often found on urinalysis and urine culture; most are asymptomatic and do not require treatment. Treatment may be required if a patient has pain symptoms, gross hematuria, lethargy, fever, and/or vomiting.

Children with NDO are usually evaluated regularly with urodynamics/video-urodynamics and ultrasound. Treatment to reduce bladder pressure (by achieving maximum detrusor pressure [PdetMax] less than 40 cm of H_2O during the storage phase) and to minimize urinary stasis in pediatric NDO patients ultimately aims to preserve the upper urinary tract. This is primarily achieved by a combination of CIC, which is recommended for all NDO children, and anticholinergic therapy for patients with high pressures or hyperreflexic bladders or vesicoureteral reflux. Approximately 10% of these pediatric patients are not adequately managed with CIC and anticholinergics (Ortho-McNeil-Janssen Pharmaceuticals 2012; Baskin 2020).

2.2. Analysis of Current Treatment Options

Table 1. Summary of Treatment Armamentarium Relevant to the Proposed Indication of Pediatric Neurogenic Detrusor Overactivity

Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA approved treatments (details adapted from referenced prescribing information)					
Oxybutynin (Ditropan) Tablet NDA 017577; Suspension NDA 018211; Ditropan XL Tablet NDA 020897	Symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder; for pediatric patients aged 5 and older	1975; 1979; 2004	Tablet: 5 mg tablet orally two times per day. Maximum dose is 5 mg three times per day. Suspension: 5 mg/5 mL (1 tsp) three times per day. Maximum dose is 1 tsp four times per day. Ditropan XL tablet: 5 mg orally once daily, not to exceed 20 mg per day	Studied in 30 children aged 5-15 with NDO using CIC. Increases in mean urine volume per catheterization from 108 to 136 mL, increase in mean urine volume after morning awakening from 148 to 189 mL, increase in mean percentage of catheterizations without a leaking episode from 34% to 51%, increase in mean cystometric capacity from 185 to 254 mL, decrease in mean detrusor pressure at maximum cystometric capacity from 44 to 33 cm H_20, reduction in percentage of patients with IDCs from 60% to 28%	Dry mouth, dizziness, somnolence, other CNS effects, urinary retention, gastric retention, decreased gastric motility, heat prostration
Solifenacin (Vesicare LS) NDA 209529	Treatment of NDO in pediatric patients aged 2 years and older	2020	Oral suspension 5 mg/mL; dosed based on weight in kg	Primary endpoint of change in maximum cystometric capacity (MCC): In children 2 to <5: MCC increased mean of 39 mL, in children 5-17, increased by a mean of 57 mL; secondary endpoint of number of incontinence episodes/24 hours: decreased by 1.6 episodes	Dry mouth, constipation, urinary tract infection, angioedema and anaphylactic reactions, urinary retention, somnolence, QT prolongation

Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Other treatments not FDA-approved for pediatric patients but used off-label					
Tolterodine (Detrol) NDA 020771 (Detrol LA) NDA 021228	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	1998	Detrol: 2 mg tablets orally twice daily Detrol LA 4 mg capsule orally once daily	Two pediatric phase 3 randomized trials with tolterodine extended release capsules. Efficacy not established. In adults: reduced number of incontinence episodes per week, number of micturitions in 24 hours and increased volume of urine voided per micturition	In pediatric patients: aggressive, abnormal, hyperactive behavior, attention disorders, UTI. General: Anaphylaxis, angioedema, urinary retention, gastric retention, dizziness, somnolence, QT prolongation, dry mouth
Fesoterodine (Toviaz) NDA 022030	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	2008	4 mg tablet orally once daily, may be increased to 8 mg once daily	Has not been established in pediatric patients. In adults, reduced number of urinary incontinence episodes per 24 hours, reduced number of micturitions in 24 hours and increased voided volume per micturition	Angioedema, urinary retention, dry mouth, constipation, decreased gastric motility, headache, dizziness, somnolence
Darifenacin (Enablex) NDA 021513	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	2004	7.5 mg tablet orally once daily, may be increased to 15 mg	Has not been established in pediatric patients. In adults, reduced average weekly urge urinary incontinence episodes, decreased average number of micturitions and increased average volume voided per micturition	Constipation, dry mouth, headache, dyspepsia, nausea, UTI, urinary retention, decreased gastric motility, somnolence
Trospium chloride (Sanctura) NDA 021595	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	2004	20 mg tablet orally twice daily	Has not been established in pediatric patients. In adults, reduced urinary frequency in 24 hours, urge incontinence episodes per week, and increased urinary void volume	Dry mouth, constipation, angioedema, urinary retention, decreased gastrointestinal motility, dizziness, confusion, hallucinations, somnolence

Source: (Ortho-McNeil Pharmaceuticals 2008; Allergan 2012; Pharmacia & Upjohn Co 2012; Warner Chilcott 2012; Pfizer Labs 2017; Pharmacia & Upjohn Co 2018; Astellas Pharma US 2020)
Abbreviations: CIC, clean intermittent catheterization; CNS, central nervous system; IDC, involuntary detrusor contraction; NDO, neurogenic detrusor overactivity; UTI, urinary tract infection

Other U.S. Food and Drug Administration (FDA)-approved drugs which have not been approved for pediatric NDO but are used off-label include: mirabegron, tolterodine, fesoterodine, darifenacin and trospium chloride. Pediatric NDO children may not have an adequate response to anticholinergics or may not tolerate them due to adverse reactions such as dry mouth, headaches, intestinal symptoms such as constipation, dizziness and somnolence, among others.

Several surgical procedures are used to manage neurogenic bladder; these are directed at preventing renal complications, promoting continence, and facilitating self-catheterization. In-utero repair of myelomeningocele is performed in specialized centers. Bladder augmentation is performed in individuals who, despite CIC and anticholinergic medications, continue to have very high bladder pressure and need a larger bladder capacity to reduce this pressure, and thus preserve their renal function. Other surgeries can include but are not limited to bladder neck/outlet surgery. Surgery carries inherent risks and is therefore reserved for when medical options are no longer effective. Risks of bladder augmentation surgery can include:

- Early complications such as postoperative ileus, transient urinary fistula, wound infection, bleeding requiring reoperation and thromboembolic complications.
- Late complications such as metabolic disturbances (reabsorption of acid and secretion of bicarbonate by the bowel segment causing acid-base and electrolyte disturbance, varying degrees of villous atrophy, occasional hypokalemia, hypochloremic hyponatremic alkalosis, hematuria-dysuria), peptic ulceration of the bladder, perforation of the gastric segment, diverticulization of the intestinal patch, urinary stone formation, risk of malignancy, perforation, bowel disturbances and a need for repeat urological surgery (Cetinel et al. 2016).

BOTOX is a sterile, vacuum-dried purified botulinum toxin type A. It is produced from (b) (4) Botulinum toxin prevents muscular contraction by inhibiting release of acetylcholine at the neuromuscular junction. Botulinum toxin type A has been shown to reduce bladder pressures in the neurogenic bladder. Acetylcholine is the predominant neurotransmitter involved in parasympathetic nerve control of the detrusor muscle. Other potential mechanisms of action which remain poorly understood include a decrease in afferent (sensory) nerve signaling during bladder filling or an affect other ATP-mediated extracellular signaling mechanisms involved in bladder sensation and function.

Per the Prescribing Information for BOTOX (Allergan 2020), the two main adverse reactions after Botulinum toxin type A injection for the treatment of adult NDO and overactive bladder (OAB) are urinary tract infection urinary tract infection (UTI) and incomplete bladder emptying or urinary retention. The most significant safety concern related to the use of BOTOX is the possibility of distant spread of toxin to areas remote to the injection site, particularly to the respiratory muscles. The current package insert contains a boxed warning regarding this risk, which states:

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses *[see Warnings and Precautions (5.1)]*.

BOTOX labeling advises patients be warned of, and observed for, potential muscle weakness and pulmonary collapse. Symptoms can include dysphagia, ptosis, difficulty holding up the head, leg weakness and numbness from hours to weeks after injection. Autonomic dysreflexia may also occur in adults. A small number of patients undergoing repeat treatments with Botulinum toxin type A injections will develop antibody-mediated resistance to the clostridial proteins present in commercial preparations. The risk may increase with more frequent treatment intervals or higher drug doses.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Onabotulinum toxin type A 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 (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- Prophylaxis of headaches in adult patients with chronic migraine
- Treatment of upper and lower limb spasticity in adult patients
- Treatment of upper limb spasticity in pediatric patients 2 to 17 years of age
- Treatment of lower limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy
- Treatment of cervical dystonia in adult patients
- Treatment of severe axillary hyperhidrosis
- 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

Additional commercial preparations of botulinum toxin serotypes A or B are:

- AbobotulinumtoxinA (Dysport™), indicated for the treatment of cervical dystonia and glabellar lines, upper and lower limb spasticity in adults, upper limb spasticity in pediatric patients 2 years and older (not cerebral palsy), lower limb spasticity in pediatric patients 2 years and older (biologics license application [BLA] 125274)
- IncobotulinumtoxinA (Xeomin), approved for the treatment of cervical dystonia and Blepharospasm, chronic sialorrhea, upper limb spasticity, glabellar lines (BLA 125360)
- RimabotulinumtoxinB (Myobloc®), indicated for the treatment of cervical dystonia, chronic sialorrhea in adults (BLA 103846)
  - Prabotulinumtoxina-XVFS Jeuveau BLA 761085 for glabellar lines

These different formulations of botulinum toxin are not interchangeable.

3.2. Summary of Presubmission/Submission Regulatory Activity

During the review of the application for the indication of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults, the Applicant requested a partial waiver of studies of BOTOX for urinary incontinence due to detrusor overactivity associated with a neurologic condition for patients aged 0 to 3 years, and a deferral for patients aged 3 to 17 years. The Applicant's proposal was discussed at a meeting of the Pediatric Review Committee (PeRC) on July 13, 2011. The PeRC agreed to grant a partial waiver for study of the proposed indication in patients aged 0 to 3 years, and further agreed to extend the waiver to patients <10 years. The PeRC also approved a deferral for study of BOTOX in pediatric patients aged 10 to 17 years with incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spina bifida, spinal cord injury). The Division of Urology, Obstetrics, and Gynecology, (then DRUP, now DUOG) and PeRC considered that studying patients aged 10 to 17 years with NDO was appropriate. The Applicant expressed an understanding and agreement of PeRC's recommendations in a teleconference with DRUP on July 18, 2011.

The August 24, 2011 approval for the adult NDO indication included required pediatric assessments under the Pediatric Research Equity Act (PREA, 21 USC 355c). The pediatric study requirements for ages <10 years were partially waived and with pediatric studies for patients ages $\geq$10 to $\leq$17 deferred. The two required studies were:

1. PMR-1 (2473-1) To evaluate the safety and efficacy of BOTOX in the treatment of urinary incontinence due to detrusor overactivitiy associated with a neurologic condition (e.g., spina bifida or spinal cord injury)
2. PMR-2 (2473-1) Long-term pediatric study to evaluate the safety and efficacy of BOTOX in the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spina bifida or spinal cord injury).

Table 2 below summarizes communications between the Division and the Applicant during protocol development and execution.

Table 2. Regulatory Activity/Communications Between Applicant and FDA

Date	Activity	Agreement Reached/Advice Given
July 18, 2011	Pre-approval (for adult indication) teleconference including discussions regarding proposed pediatric studies	Agency advised of studies required on patients ≥10 years and that patients aged 8 and 9 could be considered.
Feb 29, 2012 & Mar 30, 2012 May 14, 2012, June 27, 2012	New pediatric protocol submission for study 191622-120 and 191622-121 to BB-IND 012430/SN0139 & SN0141; FDA advice/IR for 191622-120 and 191622-121	**Revised ages for inclusion to be 8 to 17 years**
Feb 21, 2013	Final protocols submitted for 191622120 and 191622-121	
April 8, 2013	Advice/IRs for protocol changes	
May 8, 2013	Protocol changes/responses to IRs submitted	
June 25, 2013	Advice/IRs	
Sep 16, 2015	Deferral extension request	Applicant had submitted pediatric deferral extension request to revise milestones and to lower minimum age requirement from 8 to 5 years old and to lower sample size for study 191622-120 from 132 to 102. Rationale: to prevent worsening of bladder pressures and preserve renal function, recruitment challenges. FDA denied deferral extension. Agreed to lower age limit to age 5, did not agree to lower sample size.
Dec 19, 2015	Advice/IRs	
April 7, 2016	Advice/IRs	
Aug 31, 2017	Deferral extension request	On June 6, 2017, Applicant submitted deferral extension request for revised milestones and to lower sample size from 132 to 102 due to recruitment challenges. FDA agreed to revised milestones and to reduced sample size.
June 28, 2018	Deferral extension request	Applicant requested revised milestones for final report submission date on May 15, 2018; FDA agreed
May 14, 2019		Applicant requested revised milestones for final report submission date on March 29, 2019; FDA agreed.

Date	Activity	Agreement Reached/Advice Given
July 24, 2019		Applicant requested pre-sBLA meeting April 30, 2019; FDA sent preliminary comments. At the meeting FDA noted the data appeared adequate to support an sBLA submission, but that statistical significance was not achieved with respect to the prespecified efficacy analyses for any BOTOX dose. The Agency acknowledged that the secondary endpoints are clinically important and information on these endpoints as well as on urodynamic measurement variables should be submitted. Given that the secondary endpoints were not prespecified as "key" in the analysis, and that the data do not achieve efficacy on the prespecified primary endpoint, this remains a review issue. Advice regarding labeling was given: actual doses received should be presented in Section 8. Applicant inquired about orphan drug designation—the Agency recommended submission of a request for such.
Dec 20, 2019		Applicant requested deferral extension for revised milestones; FDA granted. Proposal to submit final study reports for 191622-120 and 191622-121 in May 2020.

Abbreviations: IR, information request

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

4.1. Office of Scientific Investigations (OSI)

DUOG usually requests routine clinical site inspections for most NDAs/BLAs and also for their supplements. The same was done for this sBLA; there were no irregularities noted in the data submitted or analyses conducted. A routine consult was sent to OSI requesting clinical site inspections for two sites:

1. Site #14403, Dr. Pawal Kroll in Poland, for Studies 191622-120 and 191622-121. This site enrolled a large number of patients and has the largest safety population.
2. Site #10007, Dr. Paul Zelkovic in New York, for Studies 191622-120 and 191622-121. This site has the largest safety population among U.S. sites.

The ongoing COVID-19 global pandemic has significantly limited ORA's ability to conduct onsite good clinical practice (GCP) inspections. Only mission-critical on-site inspections are being performed. Currently, the inspections for this application have been deemed not to be mission-critical.

Following discussions between OSI and DUOG, a decision was made that assessment of this application could proceed without GCP inspections if they were not possible before the action

due date. A post hoc analysis of the data was conducted excluding the sites designated for inspection, and the safety and efficacy findings remained the same.

4.2. Product Quality

No changes in dosage form or formulation of BOTOX are proposed in this efficacy supplement. Therefore, there are no chemistry, manufacturing, and controls (CMC) data to review for this application. See the CMC review in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)/Panorama dated January 19, 2021. The submission includes a request for categorical exclusion to perform an environmental assessment as per 21 Code of Federal Regulations (CFR) 25.31(c), as approval of the BOTOX indication is not expected to alter significantly the concentration or distribution of BOTOX in the environment. The request for categorical exclusion is granted.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This efficacy supplement extends the use of BOTOX for the pediatric population with NDO.

BOTOX administered by an intramuscular route is already approved in the pediatric population for other indications. A nonclinical study in juvenile animals was previously conducted to support pediatric dosing and is described in labeling. Therefore, no new nonclinical studies were conducted to support this application.

Per the December 23, 2020, nonclinical review submitted in DARRTS, the nonclinical review team concludes that this application is recommended for approval.

5.2. Referenced NDAs, BLAs, DMFs

For all nonclinical data submitted prior to this supplementary BLA, INDs 6432 and 12430 have been cross-referenced by the Applicant, as well as the original BLA 103000.

6. Clinical Pharmacology

6.1. Executive Summary

This submission is acceptable from a clinical pharmacology perspective. The Applicant agreed with the agency's proposed labeling language regarding immunogenicity of BOTOX in the pediatric NDO indication. ~~Strikethrough~~ is for deletion and <u>underline</u> is for addition.

"In 99 pediatric patients [redacted] (b) (4) who had a negative baseline result for binding antibodies or neutralizing antibodies and had at least one evaluable postbaseline value from one randomized double-blind study and one double-blind extension study, no patients developed neutralizing antibodies after receiving [redacted] (b) (4) 50 Units to 200 Units of BOTOX."

6.2. Summary of Clinical Pharmacology Assessment

The Applicant assessed immunogenicity in the two trials in pediatric patients with NDO. A total of 113 patients were treated in study 191622-120, receiving 50 U (n=38), 100 U (n=45), or 200 U (n=30). Of these 113 patients, 95 were enrolled into the extension study 191622-121 and 90 received at least 1 repeat treatment with BOTOX during their participation in this study.

Over the course of Studies 191622-120 and 190622-121, 12 of 108 patients who had at least one analyzable post-treatment immunogenicity sample, developed binding antibodies (BABs), and none of them tested positive for neutralizing antibodies (NABs). There were no apparent changes in the safety profile of patients based on BAB status.

6.3. Comprehensive Clinical Pharmacology Review

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 NDO population was 11.1% (12/108) and nobody tested positive for NABs.

A total of 113 pediatric patients were treated in study 191622-120. Of these 113 patients, 100 completed the study. Among those who completed study 191622-120, 95 were enrolled into the extension study 191622-121 and 90 received at least 1 repeat treatment with BOTOX during their participation in the study.

In study 191622-120, blood samples for immunogenicity testing were collected on day 1 prior to treatment, at week 12, and for patients who did not enter the extension study (191622-121), at study exit. In study 191622-121, blood samples for immunogenicity testing were collected prior to each treatment administration and at study exit.

Based on the results of 461 analyzable serum samples from 113 patients, 108 patients had at least one analyzable post-treatment immunogenicity sample. Among the 108 patients, 99 patients had a negative baseline result for BABs or NABs and had at least one evaluable postbaseline value; the remaining 9 patients either had insufficient sample for BABs or NABs testing at baseline or had non-reportable results at baseline.

Among the 108 patients, 18 patients tested positive for BABs and none tested positive for NABs. Four of the 18 patients (Subject (b) (6)) were positive for BABs at baseline (predose) and two of the 18 patients (Subject (b) (6) did not have sufficient baseline sample volume collected for BAB analysis. Therefore, 12 of the 18 patients were used as the numerator for calculation of the BAB incidence.

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

The impact of immunogenicity on efficacy parameters was not assessed as no patient was positive for NABs. There does not appear to be any effect on safety of BOTOX due to the development of BABs. Due to the lack of impact of BAB on efficacy and safety and to be consistent with the previous indications, only information related to NABs were reported in section 6.2 of the label.

Among the 113 patients, 108 had at least one analyzable post-treatment immunogenicity sample and were included in the safety analysis. Subject (b) (6) and (b) (6) were not included as numerator in the calculation of BAB incidence because they did not have a negative testing result at baseline. However, these three patients were considered BAB positive in the safety analysis because these three patients were tested positive for BAB after treatment.

See Section 8.5.4 for clinical assessment on the impact of immunogenicity on safety. Table 3 is a summary of overall number (%) of patients with adverse events by binding antibody status using pooled data from study 191622-120 and study 191622-121.

Table 3. Overall Number (%) of Participants With Adverse Events by Binding Antibody Status BOTOX-Treated Population

	BAB Positive (N=15) n(%)	BAB Negative (N=93) n(%)	Total (N=108) n(%)
All TEAEs	15 (100.0)	83 (89.2)	98 (90.7)
Treatment-Related TEAEs	4 (26.7)	28 (30.1)	32 (29.6)
Study Injection Procedure-Related TEAEs	4 (26.7)	24 (25.8)	28 (25.9)
Study Drug-related TEAEs	0	7 (7.5)	7 (6.5)
All serious TEAEs (STEAES)	3 (20.0)	16 (17.2)	19 (17.6)
Treatment-Related STEAEs	1 (6.7)	2 (2.2)	3 (2.8)
Discontinue Study due to TEAEs	0	2 (2.2)	2 (1.9)
Death	0	0	0

Only treated participants with analyzable immunogenicity samples post-baseline (after first treatment) are included in this table.
BAB Positive = Participants with at least one positive post-baseline result for Toxin-Binding Antibody.
BAB Negative = Participants with only negative post-baseline result(s) for Toxin-Binding Antibody

Source: Response to Information Request submitted on 12/02/2020.
Abbreviations: BAB, binding ant body; TEAE, treatment-emergent adverse event;

6.3.2. Analytical Methods

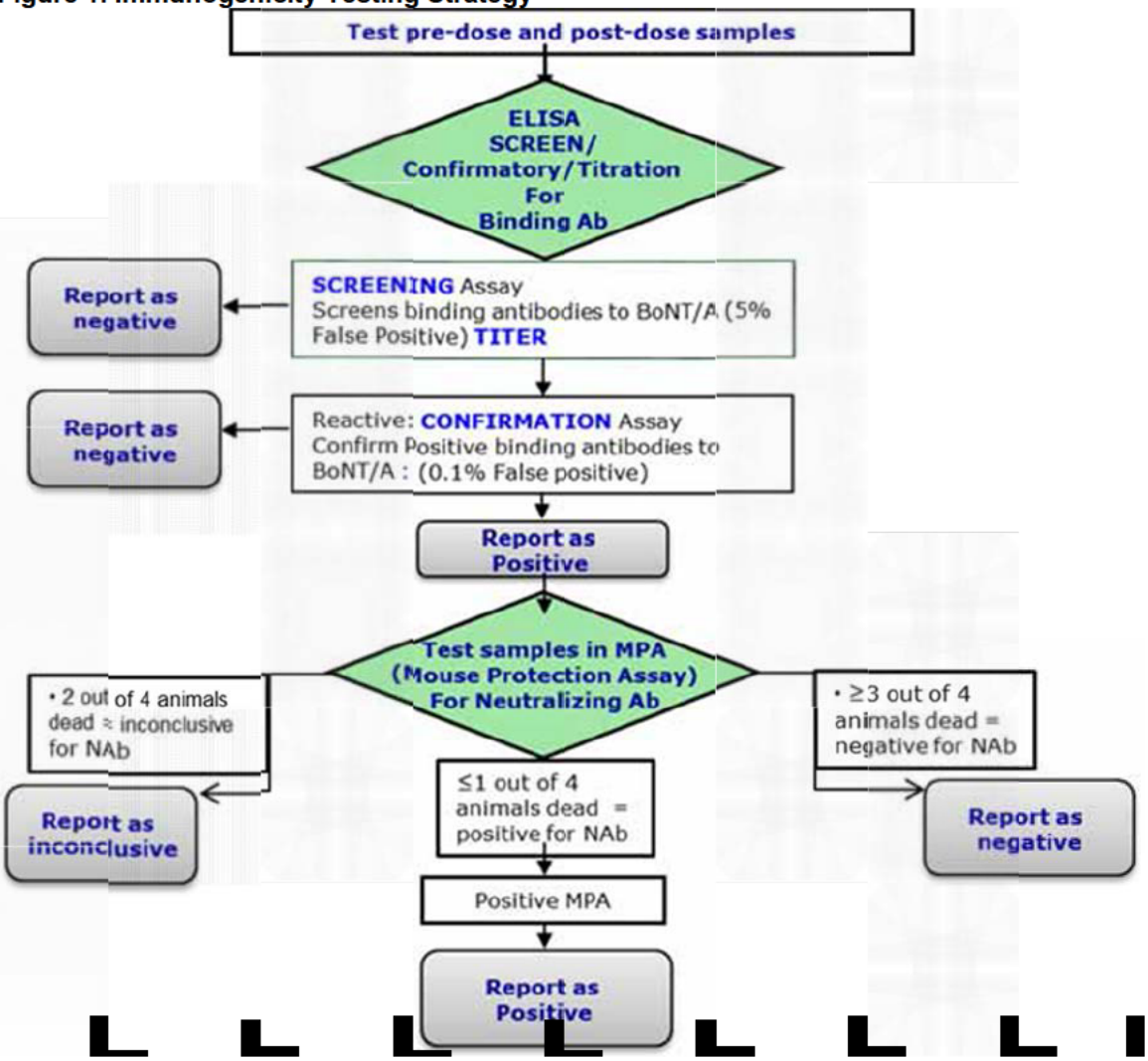
What bioanalytical methods are used to assess therapeutic protein concentrations?

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 two pediatric trials (Figure 1). The process includes an enzyme-linked immunosorbent assay (ELISA) for binding antibodies and a mouse protection assay (MPA) for neutralizing antibodies both of which are validated assays. First, results for serum BABs were analyzed using ELISA 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 MPA (provided there was sufficient serum available to analyze). Results for serum NABs were reported as protected (if they contained NABs), not protected (if they did not contain NABs), or inconclusive, and were summarized by dose and treatment cycle.

Figure 1. Immunogenicity Testing Strategy



Source: Figure 3-1 of module 2.7.1 of this submission
Abbreviations: ELISA, enzyme-linked immunosorbent assay; MPA, mouse protection assay; NAb, neutralizing ant body

According to reviewers from Office of Biotechnology Products, the Applicant used the currently approved assays. Although they introduced a new positive control and increased the freeze/thaw cycles that the control can undergo, the changes were supported by addenda submitted to the current supplement. Validation parameters of ELISA and MPA are summarized in Table 4.

Table 4. Validation Parameters of ELISA and MPA for the Qualitative Determination of Binding Antibodies and Neutralizing Antibodies to Botulinum Toxin Type A (BoNT/A) in Human Serum

			Stability					
Clinical Study	Immunogenicity Assay	Sensitivity	Room Temp. (hours)	Freeze/ Thaw Stability (No. of cycles)	Frozen (Years)	Report Number	Drug Interference	Status/ Comments
191622-120 191622-121	Anti-BoNT/A (BAB Assay)	25 ng/mL	24	10	-80°C (4.6)	AN08024-IM[a] AN08024-IM-A1[a] AN08024-IM-A2[a] AN08024-IM-A3[a] AN08024-IM-A4[a] AN08024-IM-A5 AN08024-IM-A6 AN08024-IM-A7 Module 5.3.1.4	200ng/mL	Validated
191622-120 191622-121	Neutralizing Ab (MPA Assay)	0.0234IU/mL	N/A	N/A	N/A	TX09035-TX[a] Module 5.3.1.4	N/A	Validated

BAB = binding anti-BoNT/A antibody; ELISA = enzyme-linked immunosorbent assay; MPA = mouse protection assay; N/A = not applicable; Temp. = temperature
a - previously submitted in sequence 0313, Module 5.3.1.4

Source: Table 3-1 of Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

This review includes two studies submitted by the Applicant, study 191622- 120 (providing the primary support for efficacy and safety) and study 191622-121, the long-term extension study. The two studies are described in Table 5 below. Study 191622-120 was a multicenter, double-blind, randomized, parallel group study to evaluate the efficacy and safety of three doses of BOTOX (50 U, 100 U, and 200 U) in pediatric patients 5 to 17 years of age with urinary incontinence due to NDO who had not been adequately managed with or were intolerant of anticholinergic therapy. This study did not have a placebo arm as the Applicant considered inclusion of placebo would not be medically/ethically justified. Instead, a dose of 50 U was included, as this dose was anticipated by the Applicant to be “sub-therapeutic”, based on data previously obtained in the adult NDO program (dose-ranging Phase 2 study, 191622-518) as well as the idiopathic OAB Phase 2 study 191622-077. The Applicant further quoted two published articles (Game et al. 2009; Tekgul et al. 2011) reporting doses of 300 U or up to 10 to 12 U/kg BOTOX being most commonly used to treat pediatric patients with NDO to support their belief that a dose of 50 U would be subtherapeutic.

Study 191622-121 was a multicenter, double-blind, long-term extension study to the preceding study (study 191622-120), to assess the long-term safety and efficacy of repeated treatment with three doses (50 U, 100 U, and 200 U) of BOTOX in the same pediatric patients who elected to roll over from study 191622-120. Study 191622-121 was not a randomized study, and the blinded dose received by each patient (50 U, 100 U, or 200 U BOTOX) was dependent on the assessment of the clinical response, based on efficacy and safety, to the previous blinded study treatment (50 U, 100 U, or 200 U BOTOX) by the investigators (following consultation with the

patient/parent/caregiver). The investigators/patient/caregiver could request an increase in dose in a blinded manner if deemed necessary based on the clinical response. For each study, the maximum dose permissible was 6U/kg body weight. If a patient wass assigned to a dose group that exceeded this 6U/kg limit, they would be re-assigned to the (lower) dose group that best approximated the actual dose received (study 191622-120) or not receive the increase requested dose (study 191622-121).

Table 5. Listing of Clinical Trials Relevant to This BLA

Trial Identity	NCT no.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled studies to support efficacy and safety								
191622-120	#NCT01852045	MC, R, DB, PG, Dose-ranging trial (one-time treatment at randomization and up to 48 weeks follow-up)	Three doses: BOTOX 50 U BOTOX 100 U BOTOX 200 U administered once via cystoscopy as 20 intradetrusor injections of 0.5 mL each at randomization	Primary: change from baseline in daytime average frequency of urinary incontinence episodes at Week 6	Up to 48 weeks follow-up	BOTOX 50 U / 38 BOTOX 100 U / 45 BOTOX 200 U / 30	Pediatric patients 5 to 17 years old with urinary incontinence due to NDO and had not been adequately managed with anticholinergic therapy	U.S.: 14 EU: 17
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
191622-121	#NCT01852058	MC, DB, PG, Dose-ranging extension trial to study 191622-120 (one-time treatment at randomization; from Week 12 onwards, retreatment at any scheduled clinic or telephone visit, or between scheduled visits)	Three doses: BOTOX 50 U BOTOX 100 U BOTOX 200 U administered once via cystoscopy as 20 intradetrusor injections of 0.5 mL at the beginning of each treatment cycle	Key: change from baseline in daytime average frequency of urinary incontinence episodes at Week 6 after each treatment	Up to 144 weeks follow-up	Cycle 2: 50 U / 9 100 U / 45 200 U / 36 Cycle 3: 50 U / 5 100 U / 16 200 U / 34 Cycle 4: 50 U / 3 100 U / 4 200 U / 4	Pediatric patients 5 to 17 years old with urinary incontinence due to NDO and had not been adequately managed with anticholinergic therapy	U.S.: 14 EU: 16

Source: Table 1-1 of Module 2.7.3 Summary of Clinical Efficacy
Abbreviations: DB, double-blind; MC, multicenter; NDO, neurogenic detrusor overactivity; PG, parallel group; R, randomized

7.2. Review Strategy

The efficacy review focused on individual efficacy response data from the patient bladder diary and urodynamic parameters from study 191622-120 and clinical outcomes (e.g., urinary incontinence, urine volume at first morning catheterization) from the extension study 191622-121, which the Applicant integrated into the clinical summary of efficacy. The primary efficacy endpoint was the change from baseline in number of daytime urinary incontinence episodes at Week 6 based on study 191622-120. The statistical reviewer also conducted sensitivity analyses using the Baseline Carried Forward method to impute any missing observations. Data for efficacy were further assessed at Week 12. A post hoc responder analysis was also conducted for the primary efficacy endpoint using different thresholds in reduction from baseline. Patients with missing values were counted as nonresponders for the FDA analyses. Dose-response relationships and durability of response were also assessed. The nine secondary endpoints, including urodynamic measures and patient-reported outcomes, were evaluated as change from baseline in each dose group. The primary analysis population was the modified intent-to-treat (mITT) population, which consisted of all randomized patients.

No sooner than Week 12, patients could elect to enroll in the extension study 191622-121 in which they could receive additional BOTOX treatments. Efficacy data for subsequent BOTOX injections obtained in the extension study were examined to determine whether efficacy was maintained with repeated treatment. Evaluation of these endpoints was descriptive.

8. Statistical and Clinical and Evaluation

8.1. Study 191622-120

8.1.1. Study Design

Trial Design

Study 191622-120 was a multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of three doses (50U, 100U or 200U) of BOTOX in pediatric patients age 5 to 17 years with urinary incontinence due to NDO who had not been adequately managed by at least one anticholinergic therapy. As mentioned in Section 7.1, study 191622-120 did not have a placebo arm, as this was considered medically and ethically unjustifiable, but a lower dose of 50 U was included since this dose was anticipated to be “sub-therapeutic” based on data from the adult NDO program (study 191622-518) and the idiopathic overactive bladder program (study 191622-077).

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

- 50 U BOTOX
- 100 U BOTOX
- 200 U BOTOX

Randomization was stratified by age (<12 years or ≥12 years) and baseline daytime urinary incontinence episodes (a total of ≤6 episodes or >6 episodes over the 2-day bladder diary collection period). The study medication was administered once 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 while avoiding the trigone. All patients were to receive prophylactic antibiotics prior to treatment administration on randomization/Day 1. The treatment was administered to patients under general anesthesia if patients were <12 years old; patients ≥12 years old could elect local anesthesia instead.

Patients had post-treatment follow-up visits at the study clinic at Weeks 2, 6, and 12. After that, patients had alternating telephone and clinic follow-up visits every 6 weeks until they completed the study. Patients completed the study when they qualified for retreatment (the earliest a patient could request retreatment was at Week 12), or at Week 48 if the patient never qualified for retreatment.

Key Subject Selection Criteria

Inclusion Criteria

1. Male or female, aged ≥5 years to ≤17 years of age at the time of informed consent
2. Patient has NDO based on either:
   a. Presence of an IDC during the urodynamic assessment performed in the screening period or on day 1 (prior to randomization), or
   b. Documented presence of an IDC from an historical urodynamic assessment within 12 months of screening
3. Patient has NDO due to:
   a. Spinal dysraphism [spina bifida (myelomeningocele, meningocele) and all forms of tethered cord] or
   b. Acquired NDO from a spinal cord injury, with the injury having occurred at least 6 months prior to screening, or
   c. Acquired NDO due to transverse myelitis with diagnosis at least 18 months prior to screening
4. Neurological lesion/injury at thoracic level T1 or below
5. Patient regularly using CIC to empty the bladder
   a. The CIC schedule must be at least 3 times per day
   b. CIC must have been initiated at least 3 months prior to screening

6. Total of ≥4 daytime urinary incontinence episodes over the 2-day bladder diary completed during the screening period, despite regular CIC (NOTE: If the patient has had a Mitrofanoff procedure, urinary leakage must be via the urethra.)
7. Patient has not been adequately managed with ≥1 anticholinergic agents for the treatment of NDO 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.
    a. If continuing to take anticholinergics, patients should be willing to maintain a stable dose, established prior to screening throughout the study (intravesical anticholinergics were not permitted).

Exclusion Criteria

1. An uncontrolled systemic disease, previous or current diagnosis of malignancy
2. Surgery of the spinal cord within 6 months of screening
3. History or evidence of any pelvic or urological abnormalities, except NDO, including:
    a. Bladder neck surgery resulting in an open bladder neck, or reconstructive surgery of the lower urinary tract (e.g., urinary diversion, urostomy [except for the Mitrofanoff procedure
    b. Anatomical evidence of bladder outlet obstruction, urethral, or urethral valve obstruction/stricture at screening
    c. Surgery of the urinary tract, including minimally invasive surgery (e.g., bulking agents, sling), within 6 months of screening, (except those listed above which are exclusionary for any time period
    d. Circumcision within 1 month of screening
4. Cerebral palsy
5. Uncontrolled epilepsy, defined as:
    a. More than 1 generalized seizure per month within 3 months prior to screening, or history of prolonged seizures or repetitive seizure activity requiring administration of a rescue benzodiazepine (oral, rectal, etc.) more than once a month, seizures lasting more than 10 minutes, status epilepticus, or epilepsy with autonomic involvement within 9 months prior to screening
6. History of dysphagia, aspiration pneumonia, or significant lung disease (e.g., bronchiectasis)
7. Predominance of stress incontinence, in the opinion of the investigator
8. Currently uses or plans to use a baclofen pump
9. Currently uses or plans to use an implantable or nonimplantable electrostimulation/neuromodulation device for treatment of NDO. (If a nonimplantable device is used, it must be discontinued at least 7 days prior to the first screening procedure; if a device is implanted, it must be inactive for at least 4 weeks prior to the first screening procedure; neither should be used during the study).
    a. Uses an indwelling catheter, rather than CIC, for treatment of NDO (NOTE: an indwelling catheter can be used if needed overnight, as long as it is not used during the diary collection periods)

10. Previous or current:
    a. Botulinum toxin therapy of any serotype for any urological condition, or
    b. Treatment with botulinum toxin of any serotype within 3 months of randomization/day 1 for any other condition or use
11. Intravesical capsaicin or resiniferatoxin within 12 months of screening
12. Intravesical anticholinergic within 4 weeks of screening
13. Any other medications or therapies, other than anticholinergics, to treat the symptoms of NDO within 7 days of the start of the screening period procedures and during the study
14. Known allergy or sensitivity to components of any botulinum toxin preparation, anesthetics, or antibiotics to be used during the study
15. Hemophilia, or other clotting factor deficiencies or disorders that cause bleeding diathesis
16. Cannot withhold any antiplatelet, anticoagulant therapy, or other medications with anticoagulant effects for 3 days prior to randomization/day 1. (NOTE: some medications may need to be withheld for >3 days, per clinical judgment of the investigator.)
17. Pregnant, nursing, or planning to become pregnant during the study (postmenarche female patients must also either be sexually abstinent or use another acceptable form of contraception)
18. Any medical condition that may put them at increased risk with exposure to BOTOX including diagnosed myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis
19. Current enrollment in an investigational drug or device study, or participation in such a study within 30 days of entry into this study (or longer if local requirements specify)
20. Condition or situation which in the investigator's opinion may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study.

Study Endpoints

The Applicant-defined primary efficacy endpoint was the number of daytime urinary incontinence episodes, normalized to a 12-hour daytime period, as recorded in the 2-day bladder diary during the week at Week 6 after treatment.

The Applicant-defined secondary efficacy measures included:

- Via urodynamics evaluation:
  - Maximum cystometric capacity (MCC in mL)
  - Presence/absence of an IDC
  - If an IDC is present, maximum detrusor pressure (PdetMax) during the first IDC (cm H_2O)
  - PdetMax during the storage phase (cm H_2O)
  - If a leak occurs, detrusor leak point pressure (DLPP)

A central reviewer determined the final values for these endpoints.

- Via bladder diary entries:
  - Urine volume of first morning catheterization (mL)
  - Presence/absence of night time urinary incontinence
- Other:
  - Time to patient request and time to qualification for retreatment
- Health Outcome Measures:
  - Pediatric Incontinence Questionnaire (PinQ) Score
  - Modified Treatment Benefit Scale (TBS)

None of these secondary endpoints were prespecified in the protocol to be a "key secondary endpoint" for assessment in the overall study testing.

Statistical Analysis Plan

The statistical plan was finalized before the data were unblinded. The primary analysis set was the mITT set, which included all randomized patients who received BOTOX injection on Day 1 (randomization and injection day).

The protocol-defined null hypothesis for BOTOX doses of 200 U and 100 U emphasized that there is no difference between that dose groups and the 50 U BOTOX dose group in the mean change from baseline in daily average frequency of daytime urinary incontinence episodes at week 6.

The null hypothesis was tested using an ANCOVA model with baseline value as covariate and treatment group, age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (a total of ≤6 episodes or >6 episodes over the 2-day diary collection period); and use of anticholinergic therapy (no/yes) at baseline (on day of injection) as factors. Furthermore, the last observation carried forward (LOCF) method of imputation was used to impute missing week 6 assessments. The fitted model was used to derive the adjusted mean treatment difference in the primary variable (least-squares [LS] mean difference) and associated 95% confidence interval (CI), for the comparison of the 50 U BOTOX treatment group versus the 200 U and 100 U BOTOX treatment groups.

To control for overall Type I error of testing, (two higher doses versus the lower dose for the primary efficacy endpoint), a hierarchical analysis testing strategy using a 5% significance level was prespecified, testing the 200 U group versus the 50 U group first. If this group demonstrated statistical significance then testing 100 U versus 50 U would be pursued.

For secondary endpoints, no imputation was used for the missing values of secondary efficacy variables; and no strategy to adjust for multiplicity was implemented.

Protocol Amendments

There were three protocol amendments to the original protocol (dated 14 January 2013):

- The first amendment was dated 4 October 2013. The main change was to provide clarification and guidance to investigators regarding entry criteria, study procedures, and concomitant medications/procedures. There were also a few procedures added to the protocol which included collection of an immunogenicity sample at Week 12, measurement of bladder wall thickness by ultrasound at the screening visit, addition of renal function assessment (eGFR), and volume at first IDC to be measured and recorded during urodynamics.
- The second amendment was dated 14 April 2016. The main change was to lower the minimum age to 5 years old from 8 years old and to include dosing information for a younger patient population. In addition, an update was made to the criteria for determining if a patient had a UTI. According to the protocol, an adverse event (AE) of UTI was defined as 'a symptomatic UTI that required treatment in the opinion of the investigator'. The protocol also indicated that if urinalysis/culture results were reported, which in the opinion of the investigator were considered clinically significant but did not fulfill the definition of UTI, the findings were to be recorded as AEs (e.g., bacteriuria, leukocyturia). The 'opinion of the investigator' used to justify treatment of UTI and the criteria used for qualifying 'leukocyturia' as an AE were to be described.
- The third amendment was dated 27 September 2017. The main change for this amendment was to reduce the proposed sample size from 132 to 102 due to enrollment challenges.

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant attested to compliance with good clinical practice for the two studies in accordance with the International Conference on Harmonisation (ICH) guidelines and with 21 CFR parts 50, 56, and 312.

One study site (10013, Rosalia Misseri, MD at Riley Hospital for Children, Indianapolis, IN) was closed due to issues with protocol adherence and GCP compliance. Three patients (Patients (b) (6) were screened and randomized, though one (b) (6) did not meet entry criteria. Routine monitoring visits identified problems with delays in electronic data capture entry, access to electronic medical records and other administrative and staffing concerns. The investigator was put on screening hold to allow for resolution of the issues. However, at the follow-up monitoring visit, the issues were ongoing and the Applicant closed the site. Upon review of records, the Applicant believed that the data from the three patients were not compromised and these data are included in the efficacy and safety analyses.

Of note, 12 other study sites were closed due to difficulties with recruitment, prior to screening any patients. Three sites closed after some patients were screened but before they were

randomized. Eight sites requested closure after randomization and enrollment of patients, four due to difficulty with recruitment and the volume of study paperwork, one due to loss of the study coordinator, one because their standard practice was not in line with the study protocol and one closed after database lock for study 191622-120.

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.

Financial Disclosure

Financial disclosure was made for all required studies submitted to this application. There is no evidence to suggest that a financial relationship had any impact on study results.

Patient Disposition

A total of 164 patients were screened and a total of 114 patients were enrolled and randomized into study 191622-120. Of these, 113 received study medication: 38, 45, and 30 patients were assigned 50 U BOTOX, 100 U BOTOX, and 200 U BOTOX, respectively; 100 patients completed study 191622-120. One patient in the 50 U BOTOX group was randomized but did not receive treatment because the patient had a urinary tract infection on the day of study injection. All 113 treated patients were included in the mITT population. Among these 113 patients, 14 (12.3%) discontinued the study early. Of all the discontinued patients, 6 (15.4%) were in the 50 U group, 4 (8.9%) in the 100 U group, and 4 (13.3%) in the 200 U group. Overall, the most common reason for discontinuation was “other” with 6 (5.3%) patients. While there were no patients discontinued due to adverse events or lack of efficacy in the 100 U and 200 U groups, in the 50 U group, one subject (2.6%) discontinued due to adverse events and three patients (7.7%) due to lack of efficacy. Table 6 summarizes the patient disposition.

Table 6. Study 191622-120 Patient Disposition

Disposition	BOTOX 50U n (%)	BOTOX 100U n (%)	BOTOX 200U n (%)	Total n (%)
Randomized	39 (100.0)	45 (100.0)	30 (100.0)	114 (100.0)
Treated	38 (97.4)	45 (100.0)	30 (100.0)	113 (99.1)
Completed study	33 (84.6)	41 (91.1)	26 (86.7)	100 (87.7)
Discontinued	6 (15.4)	4 (8.9)	4 (13.3)	14 (12.3)
Reason for discontinuation				
Adverse event	1 (2.6)	0	0	1 (0.9)
Lack of efficacy	3 (7.7)	0	0	3 (2.6)
Lost to follow-up	0	1 (2.2)	1 (3.3)	2 (1.8)
Withdrawal by subject	1 (2.6)	0	1 (3.3)	2 (1.8)
Other	1 (2.6)	3 (6.7)	2 (6.7)	6 (5.3)

Source: Table 10-1 of study 191622-120 Study Report.

Due to the 6 U/kg dosing cap, as prespecified in the protocol, patients who received less than their randomized dose due to their weight and the dose limit of 6 U/kg were analyzed to the nearest dose group based on the dose they received (as presented in Table 7). Therefore, several patients were assigned to a different treatment group for analysis than the group to which they were randomized.

Table 7. BOTOX Treatment Groups Based on Actual Dose Administered

Actual Dose Administered	BOTOX Treatment Group
<75 U	50 U BOTOX
≥75 U and <150 U	100 U BOTOX
≥150 U	200 U BOTOX

Source: Table 1 of the Statistical Analysis Plan (SAP) for study 191622-120.

According to the Applicant, five (5) patients originally randomized to the 200 U BOTOX group were re-assigned to the 100 U BOTOX group, for analysis purposes, based on actual dose received due to the 6 U/kg cap (Patients (b) (6) [96 U], (b) (6) [108 U], (b) (6) [108 U], (b) (6) [120 U], and (b) (6) [144 U]); one patient originally randomized to the 200 U BOTOX group was re-assigned to the 50 U group (Patient (b) (6) [72 U]); three patients randomized to the 200 U BOTOX group received a lower dose but remained in the 200 U BOTOX group (Patients (b) (6) [180 U], (b) (6) [180 U] and (b) (6) [168 U]); and one patient randomized to the 100 U BOTOX group received a lower dose but remained in the 100 U BOTOX group (Patient (b) (6) [96 U]).

Protocol Violations/Deviations

The most commonly reported protocol deviations were:

- Stratification errors due to correction of patient diary recording errors (15/114, 13.1%)
- No record of patient being inadequately managed with anticholinergic agents (11/114, 9.6%)
- Incorrect baseline daytime urinary incontinence episodes recorded into the Interactive Voice Response System (IVRS) system at randomization, leading to patient being randomized into the incorrect stratum and being dosed (10/114, 8.8%)
- Patient had <4 daytime urinary incontinence episodes over the 2-day bladder diary completed during screening (5/114, 4.4%)
- Significant deviation in patient diary completion, mostly due to the bladder diary not being completed at the Week 6 visit (4/114, 3.5%)
- Stratification errors missed before database lock (7/114, 6.1%)
- 2/114 (1.8%) had a significant deviation in the consent process (assent form not signed or both parents did not sign consent form)
- One patient was not captured as a protocol deviation thought they should have been—they did not receive the correct dose (received 200 U when they should have received 180 U due to 6U/kg weight cap)

Forty study patients had at least one significant protocol deviation.

***Clinical Reviewer's Comment**: these protocol violations/deviations did not significantly alter the safety and efficacy findings of the study.*

Table of Demographic Characteristics

Demographic and baseline characteristics were generally balanced among the three treatment groups except that 100 U group had more male than female patients. Most were White (over 75%); there were slightly more males (57.5%) than females; and the mean age of the patients was approximately 11 years old with similar percentage of patients (approximately 50%) in both the <12 years old group and ≥12 years old group.

Table 8. Study 191622-120 Demographic Characteristics

Demographic Parameters	BOTOX 50U (N=38) n (%)	BOTOX 100U (N=45) n (%)	BOTOX 200U (N=30) n (%)	Total (N=113) n (%)
Sex				
Male	20 (52.6)	30 (66.7)	15 (50.0)	65 (57.5)
Female	18 (47.4)	15 (33.3)	15 (50.0)	48 (42.5)
Age				
Mean years (SD)	11.4 (3.50)	10.8 (3.26)	11.9 (3.13)	11.3 (3.31)
Median (years)	11	11	12	11
Min, max (years)	5.0, 17.0	5.0, 16.0	6.0, 17.0	5.0, 17.0
Age group				
<12 years	20 (52.6)	26 (57.8)	12 (40.0)	58 (51.3)
≥12 years	18 (47.4)	19 (42.2)	18 (60.0)	55 (48.7)
Race				
White	29 (76.3)	34 (75.6)	22 (73.3)	85 (75.2)
Black or African American	6 (15.8)	3 (6.7)	2 (6.7)	11 (9.7)
Asian	1 (2.6)	2 (4.4)	1 (3.3)	4 (3.5)
Hispanic	1 (2.6)	3 (6.7)	3 (10.0)	7 (6.2)
Other[1]	1 (2.6)	3 (6.7)	2 (6.7)	6 (5.3)
Weight (kg)				
Mean (SD)	41.91 (18.10)	40.08 (23.54)	46.87 (15.32)	42.52 (19.82)
Median	40.60	32.30	45.70	41.10
Min, max	12.9, 87.7	15.8, 127.9	27.6, 109.8	12.9, 127.9
Height (cm)				
Mean (SD)	136.61	135.47	142.78	137.78
Median	131.00	134.50	146.00	137.00
Min, max	95.5, 175.0	95.0, 174.0	116.3, 170.0	95.0, 170.0

Source: Table 10-4 of study 191622-120 CSR.
Abbreviations: SD, standard deviation

***Clinical Reviewer's Comment**: The study population included children ages 5 to 17 years with a wide range of body weights; however the mean age was 11.3 years old, and the mean body weight was 42.52 kg. This indicates that the average child in the study would have had symptomatic NDO for a number of years, tried first line treatment options unsuccessfully and was appropriate for a second line therapy which requires an invasive procedure. The study population included slightly more males. The study population included a majority of White patients, reflecting the demographics of the study sites, more than half of which were in Europe. Subgroup analyses of these groups were performed and are described in Sections 9.1 and 9.3.7.*

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

Other baseline disease characteristics for the mITT population are presented in the following table, they were generally balanced among the three treatment groups.

Table 9. Study 191622-120 Other Baseline Characteristics

Characteristics	BOTOX 50U (N=38)	BOTOX 100U (N=45)	BOTOX 200U (N=30)	Total (N=113)
Stratification, n (%)				
Age <12 years, daytime UI ≤6	10 (26.3)	17 (37.8)	8 (26.7)	35 (31.0)
Age <12 years, daytime UI >6	10 (26.3)	9 (20.0)	4 (13.3)	23 (20.4)
Age ≥12 years, daytime UI ≤6	12 (31.6)	8 (17.8)	10 (33.3)	30 (26.5)
Age ≥12 years, daytime UI >6	6 (15.8)	11 (24.4)	6 (20.0)	23 (20.4)
Missing	0 (0.0)	0 (0.0)	2 (6.7)	2 (1.8)
Neurologic characteristics, n (%)				
Spinal dysraphism	33 (86.8)	39 (86.7)	27 (90.0)	99 (87.6)
Spinal cord injury	5 (13.2)	6 (13.3)	2 (6.7)	12 (11.5)
Transverse myelitis	0 (0.0)	0 (0.0)	1 (3.3)	1 (0.9)
Daily average frequency of daytime UI episodes[1]				
Mean (SD)	2.81 (1.05)	2.99 (1.07)	3.75 (5.24)	3.12 (2.78)
Median	2.65	2.80	2.70	2.80
Min, max	0.8, 6.7	1.3, 6.1	0.5, 29.5	0.5, 29.5
n	38	45	28	111
Urine volume at first morning catheterization (mL)				
Mean (SD)	203.46 (167.48)	164.19 (114.48)	187.69 (135.71)	183.70 (139.85)
Median	147.50	132.50	170.00	150.00
Min, max	25.0, 725.0	24.5, 465.0	7.5, 500.0	7.5, 725.0
n	38	44	27	109
Night time urinary incontinence, n(%)				
Yes	38 (100.0)	39 (86.7)	27 (90.0)	104 (92.0)
No	0	6 (13.3)	1 (3.3)	7 (6.2)
Missing	0	0	2 (6.7)	2 (1.8)
MCC (mL)				
Mean (SD)	169.11 (106.26)	179.19 (130.08)	202.33 (121.36)	181.66 (119.77)
Median	136.00	144.00	176.00	151.00
Min, max	19.0, 500.0	33.0, 643.0	34.0, 500.0	19.0, 643.0
n	36	43	27	106
PdetMax (cm H_2O) during the storage phase				
Mean (SD)	58.22 (29.45)	56.48 (26.86)	56.70 (33.89)	57.13 (29.40)
Median	54.00	53.00	54.00	54.00
Min, max	13.0, 145.0	10.0, 128.0	22.0, 174.0	10.0, 174.0
n	36	42	27	105
PdetMax1stIDC (cm H_2O) (if IDC present)				
Mean (SD)	34.88 (31.67)	29.27 (26.77)	22.44 (16.63)	29.42 (26.64)
Median	20.0	19.0	16.0	19.0
Min, max	5.0, 113.0	3.0, 128.0	7.0, 72.0	3.0, 128.0
n	33	37	25	95

Source: Table 10-5 of study 191622-120 CSR.
[1] Normalized to a 12-hour period
Abbreviations: IDC, involuntary detrusor contraction; MCC, maximum cystometric capacity; PdetMax, maximum detrusor pressure; PdetMax1stIDC, PdetMax during the first IDC; SD, standard deviation; UTI, urinary tract infection

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

According to the Applicant, of the 114 patients randomized, 1 patient in the 50 U BOTOX group was randomized but did not receive treatment. Of the 113 patients who received study medication on Day 1, all but 5 received their study medication in accordance with the protocol. Four patients (Patients [redacted] (b) (6)) were injected in locations other than, or in addition to, the location specified by the injection paradigm in the protocol; however, all 4 received the correct number of injections (20), volume of study medication (10 mL), and correct dose. In addition, one patient was injected per protocol but did not receive the correct dose. Due to the 6 U/kg cap this patient should have received 180 U BOTOX (based on a rounded weight of 31 kg), however they actually received 200 U BOTOX.

Anticholinergic therapy has been used by 102 out of the 113 treated patients (90.3%) prior to study enrollment. The proportion of patients deemed inadequately managed by anticholinergic therapies due to inadequate efficacy response was 84% (95/113) and due to adverse effects were 14% (16/113); patients could have more than one reason for their inadequate management. The Applicant reported that 11 patients did not have prior anticholinergic use recorded. Patients who were receiving anticholinergic medication at baseline were permitted to continue taking their anticholinergic medication throughout the study at a stable dose. The use of other medications or therapies (other than anticholinergics) to treat the symptoms of NDO within 7 days of the start of the screening period procedures and during the study was prohibited. At baseline, use of anticholinergic therapy in the mITT population was recorded for 54.9% (62/113) of patients; anticholinergic use at baseline was lower in the 200 U BOTOX group (11/30, 36.7%). The Applicant further reported that during the study, the most commonly used classes of medications other than anticholinergic therapies were first generation cephalosporins (47.8% of patients), opioid anesthetics (43.4%), and other general anesthetics (40.7%).

Efficacy Results – Primary Endpoint

Study 191622-120 demonstrated a similar magnitude of decrease from baseline to Week 6 in the normalized daily average frequency of daytime urinary incontinence episodes for all 3 BOTOX treatment groups. The lower bound of the 95% confidence interval for this measurement for each dose group excluded zero at Weeks 2, 6 and 12. The magnitude of decrease at the other post-treatment timepoints (Weeks 2 and 12) were also similar, with no significant difference between the 200 U BOTOX group (or 100 U BOTOX group) and the 50 U BOTOX group (See Table 10).

Table 10. Study 191622-120 Change From Baseline (CFB) in Daytime Average Frequency of Urinary Incontinence Episodes (mITT)

Timepoint	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Differences (95% CI)	200 U vs. 50 U Differences (95% CI)
Baseline	2.81 (1.05)	2.99 (1.07)	3.68 (5.07)		
Week 2[1]	-1.19 (-1.64, -0.74)	-1.00 (-1.41, -0.59)	-1.12 (-1.66, -0.58)	0.19 (-0.41, 0.80)	0.07 (-0.63, 0.77)
Week 6[1]	-1.30 (-1.71, -0.90)	-1.30 (-1.68, -0.93)	-1.34 (-1.82, -0.85)	0.00 (-0.55, 0.55)	-0.04 (-0.67, 0.60)
Week 12[1]	-1.17 (-1.62, -0.72)	-1.39 (-1.79, -0.98)	-0.92 (-1.45, -0.39)	-0.22 (-0.81, 0.38)	0.25 (-0.45, 0.95)

Source: Table 14.2-1.1 of study 191622-120 CSR.
[1] Least squares estimate and contrast t-test comparing specified treatment groups, are based on ANCOVA model with baseline value as covariate and treatment group, age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (<=6 or >6) and anticholinergic therapy (yes/no) at baseline as factors.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat

It is noted that daytime urinary incontinence episodes at study baseline was higher in the 200 U BOTOX group (3.68) than the 50 U and 100 U BOTOX groups (2.81 and 2.99, respectively), due to 1 patient (Patient (b) (6)) who had a very high frequency of average daytime urinary incontinence episodes at baseline (29.5 daytime urinary incontinence episodes). The statistical reviewer analyzed the primary efficacy endpoint excluding this one outlier. The statistical reviewer also conducted sensitivity analyses using the Baseline Carried Forward method to impute any missing observations. Both sensitivity analyses yielded similar results as the primary efficacy analysis (See Table 11).

In addition, the Applicant conducted sensitivity analyses using a median imputation method for missing data up to Week 6, non-normalized urinary incontinence data with LOCF imputation, and a mixed effects model with repeated measures; the results of these sensitivity analyses were also consistent with the primary efficacy results.

Table 11. Study 191622-120 Sensitivity Analyses of Change From Baseline in Daytime Average Frequency of Urinary Incontinence Episodes at Week 6

Parameter	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Differences (95% CI)	200 U vs. 50 U Differences (95% CI)
Baseline	2.81 (1.05)	2.99 (1.07)	3.68 (5.07)		
Excluding 1 outlier from 200 U[1]	-1.08	-1.10	-1.10	-0.02 (-0.57, 0.52)	-0.02 (-0.65, 0.62)
Baseline carried forward[1]	-1.20	-1.28	-1.22	-0.07 (-0.68, 0.52)	-0.02 (-0.71, 0.68)

Source: Statistical Reviewer's Analysis.
[1] Least squares estimate and contrast t-test comparing specified treatment groups, are based on ANCOVA model with baseline value as covariate and treatment group, age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (≤6 or >6) and anticholinergic therapy (yes/no) at baseline as factors.
Abbreviations: CI, confidence interval

The Applicant conducted a responder analysis of the primary efficacy endpoint using different thresholds in reduction from baseline (at least 50%, 75%, 90%, and 100%) in daytime urinary incontinence episodes post-treatment. The Applicant's analysis was based on the number of patients with nonmissing values at Week 6; the statistical reviewer analyzed these data where

patients with missing values were considered as nonresponders. Based on the statistical reviewer's analysis, at Week 6, the proportion of patients who had at least 50% reduction from baseline in daytime urinary incontinence episodes were 44.7%, 48.9%, and 46.7% in the 50 U, 100 U, and 200 U groups respectively; the proportion of patients who had 100% reduction from baseline in daytime urinary incontinence episodes were 23.7%, 22.2%, and 23.3% in the 50 U, 100 U, and 200 U groups respectively. The responder analysis results were consistent with the primary efficacy analysis results: there were no significant difference between the 100 U or 200 U BOTOX group compared with the 50 U group.

Table 12. Study 191622-120 Proportion of Patients With Various Thresholds of Reduction From Baseline in Normalized Daytime Urinary Incontinence Episodes at Week 6 (mITT)

Proportion	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Differences (95% CI)	200 U vs. 50 U Differences (95% CI)
50%	17 (44.7)	22 (48.9)	14 (46.7)	4.1 (-17.4, 25.7)	1.9 (-21.9, 25.8)
75%	10 (26.3)	16 (35.6)	11 (36.7)	9.2 (-10.6, 29.0)	10.4 (-11.9, 32.6)
90%	9 (23.7)	11 (24.4)	8 (26.7)	0.8 (-17.7, 19.2)	3.0 (-17.8, 23.8)
100%	9 (23.7)	10 (22.2)	7 (23.3)	-1.5 (-19.6, 16.7)	-0.4 (-20.6, 19.9)

Source: Statistical Reviewer's Analysis.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat

***Clinical Reviewer's Comment**: We acknowledge that there were no statistically significant differences between the higher doses and the 50U dose, the assumed "sub-therapeutic" dose, in the prespecified primary analysis. One could conclude either the BOTOX doses were equally ineffective or all of the doses were equally effective. To conclude the former would require the establishment that the BOTOX 50U is ineffective (a true placebo), which is not the case. The Applicant reasonably assumed that such dose was "subtherapeutic" based on adult OAB and NDO data. But these adult populations, including adult NDO, differ in pathophysiology and clinical course from the pediatric NDO population. Therefore, one could not establish that the 50U dose is similarly "sub-therapeutic" or ineffective in pediatric NDO patients. Also, NDO children do not spontaneously improve in their urinary clinical or urodynamic outcomes without treatment. This is reflected in the fact that the study design for anticholinergics intended for the treatment of pediatric NDO was uncontrolled and open-label. The approval of these medications relied on findings of within-group positive (beneficial) changes from baseline in important urodynamic and clinical endpoints that excludes zero in the lower bound of the 95% confidence interval around their mean estimates. From a clinical perspective and based on the above discussion, we determine that all 3 doses are effective. The study patients failed anticholinergic therapy, although over half remained on such treatment at baseline. Despite this treatment-resistant group, all 3 doses of BOTOX exerted a treatment magnitude (approximately 40% reduction from baseline in number of incontinence episodes, the proportion of responders) that was clinically meaningful. Furthermore, the lower bound of the 95% confidence interval around the mean changes in the primary endpoint for each dose group excluded zero at Weeks 2, 6, and 12. Evaluated similarly to the approved anticholinergic medications, where positive change from baseline is considered a demonstration of drug benefit, we conclude the same for the 3 BOTOX doses.*

Efficacy Results – Secondary and Other Relevant Endpoints

There was no predefined Type I error control for testing any secondary endpoints. With nine secondary endpoints testing two dose levels and some tested at multiple time points (Weeks 2, 6, and 12), the Type I error (false positive) rate would be inflated and any conclusion about whether effectiveness has been demonstrated based on one or two favorable secondary endpoints findings becomes unreliable. Therefore, any findings for secondary endpoints are more exploratory in nature from statistical perspective.

The Applicant defined a number of secondary efficacy measures without specifying which were key ones. Among the secondary efficacy measures, there were six urodynamics parameters. The results of these six parameters at Week 6 are presented in Table 13.

Urodynamic Endpoints:

PdetMax during the storage phase: All 3 dose groups showed an improvement from baseline in this urodynamic measurement, and the improvement appeared to be dose-related. The estimated treatment difference between BOTOX 200 U and the 50 U groups was -14.43 (95% CI: [-26.06, -2.79]), a difference that reached nominal statistical significance. The estimated treatment difference between the BOTOX 100 U and 50 U groups was -7.21 (95% CI [-17.65, 3.24]), which did not reach nominal statistical significance.

Others: All dose groups showed a positive (improvement) change from baseline in the other five urodynamic parameters, with all having a 95% confidence interval excluding zero except for maximum detrusor pressure during the first IDC with the 50U and 200 U doses. These treatment effects on these parameters did not appear to be dose-related as there were no notable differences among the three treatment groups.

Table 13. Study 191622-120 Summary of Secondary Efficacy Urodynamics Parameters at Week 6 (mITT)

Secondary Endpoint	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Differences (95% CI)	200 U vs. 50 U Differences (95% CI)
Maximum detrusor pressure during the storage phase					
Baseline (SD)	58.22 (29.45)	56.48 (26.86)	56.70 (33.89)		
CFB at Week 6 (SD)	-12.88 (3.79)	-20.09 (3.63)	-27.31 (4.56)		
95% CI	(-20.4, -5.3)	(-27.3, -12.9)	(-36.4, -18.2)	-7.21 (-17.65, 3.24)	-14.43 (-26.06, -2.79)
Maximum cystometric capacity (MCC) (mL)					
Baseline (SD)	169.11 (106. 26)	179.19 (130.08)	202.33 (121.36)		
CFB at Week 6 (SD)	62.06 (14.34)	48.57 (13.55)	63.55 (17.36)		
95% CI	(33.5, 90.6)	(21.6, 75.5)	(29.0, 98.1)	-13.49 (-52.61, 25.63)	1.49 (-43.01, 45.99)
MCC as a proportion of EBC					
Baseline (SD)	0.40 (0.28)	0.51 (0.32)	0.53 (0.28)		
Week 6 (SD)	0.15 (0.04)	0.14 (0.04)	0.18 (0.05)		
95% CI	(0.1, 0.2)	(0.1, 0.2)	(0.1, 0.3)	-0.01 (-0.12, 0.09)	0.03 (-0.09, 0.15)
Proportion of patients with an IDC					
Baseline (SD)	34/36 (94.4%)	37/42 (88.1%)	25/27 (92.6%)		
Week 6 (SD)	21/34 (61.8%)	17/38 (44.7%)	13/28 (46.4%)		
95% CI	(43.6, 77.8)	(28.6, 61.7)	(27.5, 66.1)	0.7 (0.45, 1.14)	0.8 (0.40, 1.21)
Maximum detrusor pressure during the first IDC					
Baseline (SD)	34.88 (31.67)	29.27 (26.77)	22.44 (16.63)		
CFB at Week 6(SD)	-7.64 (5.3)	-12.13 (5.57)	-5.46 (8.27)		
95% CI	(-18.4, 3.1)	(-23.4, -0.9)	(-22.2, 11.3)	-4.49 (-19.65, 10.67)	2.18 (-18.43, 22.80)
Detrusor leak point pressure (DLPP) (cm H2O)[2]					
Baseline (SD)	42.00 (12.28)	46.00 (38.00)	25.50 (2.12)		
Mean at Week 6	45.60 (14.54)	37.11 (17.94)	35.80 (29.00)		
CFB at Week 6 (SD)	9.50 (2.12)	-39.0	12.0		
95% CI	(-9.6, 28.6)	-	-		

Source: Tables 11-5 to 11-10 of study 191622-120 CSR.
[1] Least squares estimate and contrast t-test comparing specified treatment groups, are based on ANCOVA model with baseline value as covariate and treatment group, age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (≤6 or >6) and anticholinergic therapy (yes/no) at baseline as factors.
[2] Due to the low numbers of patients who recorded both a baseline and postbaseline DLPP during urodynamics (only 1 or 2 patients in each treatment group), no ANCOVA analysis on the change from baseline was performed on these data, and consequently no meaningful conclusions can be drawn.
Abbreviations: CI, confidence interval; EBC, estimated bladder capacity; IDC, involuntary detrusor contraction; mITT, modified intent-to-treat; SD, standard deviation

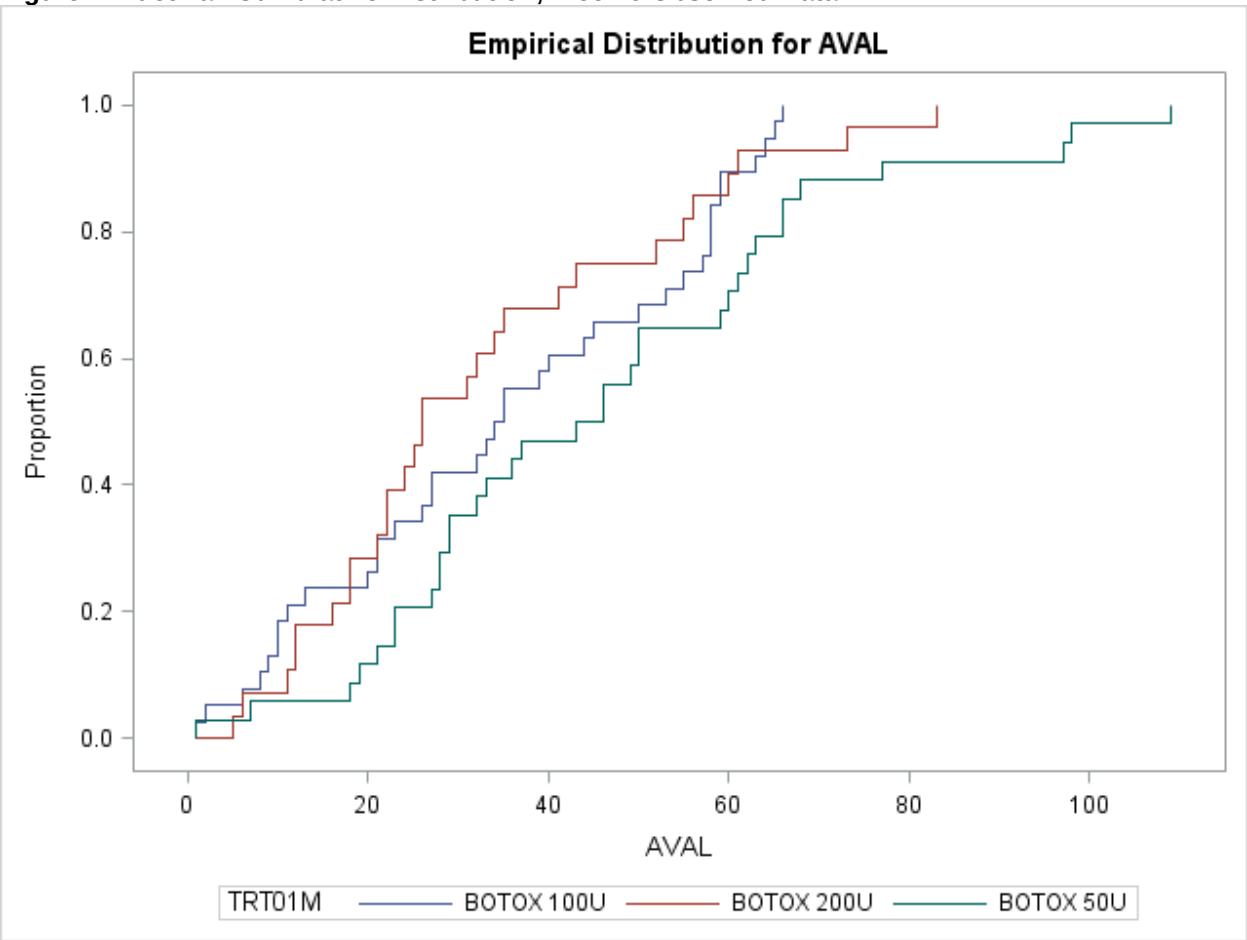
The statistical reviewer also conducted a responder analysis and created cumulative distribution curves of PdetMax at Week 6, where the clinical team defined a responder as a patient with an absolute PdetMax measurement of <40 cm H_20 on treatment based on observed data. This finding is clinically significant because this is generally a urodynamic treatment goal for minimizing upper urinary tract deterioration and also as a threshold for treatment decisions in NDO children. The 200 U BOTOX dose numerically had the highest proportion of patients whose PdetMax was reduced below 40 cm H_20 at Week 6. The difference between the 200U dose group and the 50U group was nominally statistically significant.

Table 14. Responder Analysis Maximum Detrusor Pressure During the Storage Phase, Week 6, Observed Data

Parameter	BOTOX 50 U (N=34) n (%)	BOTOX 100 U (N=38) n (%)	BOTOX 200 U (N=28) n (%)	100 U vs. 50 U Difference (95% CI)	200 U vs. 50 U Difference (95% CI)
Responder	16 (47.1)	22 (57.9)	19 (67.9)	10.8 (-12.1, 33.8)	20.8 (-3.3, 44.9)
Nonresponder	18 (52.9)	16 (42.1)	9 (32.1)		

Source: Created by Statistical Review Team
Abbreviations: CI, confidence interval

Figure 2. PdetMax Cumulative Distribution, Week 6 Observed Data



Source: Created by Statistical Review Team
Abbreviations: PdetMax, maximum detrusor pressure

Clinical Endpoints:

Night time urinary incontinence and urine volume at first morning catheterization: The Applicant also analyzed presence/absence of night time urinary incontinence and urine volume at first morning catheterization. At the primary timepoint of Week 6, all three dose groups showed improvement from baseline in night time urinary incontinence episodes and had similar proportion of patients who were incontinence-free at night. By Week 12, there was some decline in all 3 BOTOX treatment groups in the proportion of patients incontinence-free at night compared to Week 6 (see Table 15).

Table 15. Study 191622-120 Summary of Night Time Urinary Incontinence by Visit (mITT)

Secondary Endpoint Incontinence Episodes	BOTOX 50 U (N=38) n/N (%)	BOTOX 100 U (N=45) n/N (%)	BOTOX200 U (N=30) n/N (%)
Baseline			
0	0/38 (0.0)	6/45 (13.3)	1/28 (3.6)
1	5/38 (13.2)	1/45 (2.2)	4/28 (14.3)
2	33/38 (86.8)	38/45 (84.4)	23/28 (82.1)

Secondary Endpoint Incontinence Episodes	BOTOX 50 U (N=38) n/N (%)	BOTOX 100 U (N=45) n/N (%)	BOTOX200 U (N=30) n/N (%)
Week 6			
0	11/36 (30.6)	14/43 (32.6)	14/43 (32.6)
1	6/36 (16.7)	7/43 (16.3)	7/43 (16.3)
2	19/36 (52.8)	22/43 (51.2)	22/43 (51.2)
Week 12			
0	11/36 (30.6)	8/42 (19.0)	6/28 (21.4)
1	6/36 (16.7)	7/42 (16.7)	4/28 (14.3)
2	19/36 (52.8)	27/42 (64.3)	18/28 (64.3)

Source: Table 11-4 of study 191622-120 CSR.
Abbreviations: mITT, modified intent-to-treat

At the primary timepoint of Week 6, all three dose groups increased from baseline the urine volume at first morning catheterization, and this treatment effect appeared dose-related. The increase in urine volume observed in the 200 U BOTOX group was numerically higher than the 50 U group with an estimated treatment difference of 65.56 mL (95% CI: [52.15, 122.84]); this was nominally statistically significant. At Week 12, the increase observed in the 100 U BOTOX group was numerically higher compared to the 50 U dose with an estimated treatment difference of 42.89 (95% CI: [3.06, 82.71]); this was nominally statistically significant. See Table 16 below.

Table 16. Study 191622-120 Summary of Urine Volume at First Morning Catheterization (mITT)

	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Differences (95% CI)	200 U vs. 50 U Differences (95% CI)
Baseline	203.46 (167.48)	164.19 (114.48)	187.69 (135.71)		
CFB at Week 6	21.93 (14.68)	34.90 (13.58)	87.49 (17.81)	12.97 (-26.12, 61.86)	65.56 (52.15, 122.84)
CFB at Week 12	12.88 (15.12)	55.77 (13.71)	45.22 (17.75)	42.89 (3.06, 82.71)	32.34 (-13.83, 78.50)

Source: Tables 11-3 of study 191622-120 CSR.
Abbreviations: CFB, change from baseline; CI, confidence interval; mITT, modified intent-to-treat

Clinical Reviewer's Comment: *The increase in urine volume at first morning catheterization was seen with all three BOTOX doses. It is clinically significant as it demonstrates an increase in bladder capacity.*

Post Hoc Analysis of Efficacy Endpoints for 6U/kg but Less Than 200 U Total Dose

Compared to the lower doses, the BOTOX 200 U dose had the additional benefit on PdetMax and this dose would appear to be the most beneficial dose. However, we recognized that the maximum allowed dose in this study was 6U/kg and that lighter weight children would not be eligible for treatment with 200 U. At our request, the Applicant conducted a post hoc efficacy analysis on the group of patients who received less than their assigned BOTOX dose due to the 6U/kg weight cap. This group consisted only of 10 patients. The efficacy results for the primary

endpoint and select secondary endpoints are similar to those for the dose groups studied (50 U, 100 U, 200 U).

Table 17. Study 191622-120 Baseline and Change From Baseline in Select Endpoints for Patients who Received Less Than Their Assigned Dose Due to the Weight Cap

Endpoint	Patients who Received Less Than Their Assigned BOTOX Dose Due to the Weight Cap N=10
Daily average frequency of daytime urinary incontinence episodes	
Mean baseline	2.5
Mean change* at Week 2 (95% CI)	-0.7 (-1.6, 0.2)
Mean change* at Week 6** (95% CI)	-1.0 (-1.7, -0.2)
Mean change* at Week 12 (95% CI)	-0.8 (-1.7, 0.1)
Urine volume at first morning catheterization (mL)[b]	
Mean baseline	102.0
Mean change* at Week 2 (95% CI)	74.7 (-7.6, 157.0)
Mean change* at Week 6** (95% CI)	62.9 (-1.2, 127.0)
Mean change* at Week 12 (95% CI)	86.6 (-0.3, 173.4)
Maximum detrusor pressure (PdetMax) during the storage phase (cm H_2O)[b]	
Mean baseline	54.3
Mean change* at Week 6** (95% CI)	-25.5 (-48.9, -2.1)
Maximum cystometric capacity (mL) (MCC)[b]	
Mean baseline	140.3
Mean change* at Week 6** (95% CI)	61.5 (10.1, 112.9)

Source: Table 19 Module 1.11.3 Clinical Information Amendment SDN 436 BLA 103000
Abbreviations: CI, confidence interval

Dose/Dose Response

The area under the curve (AUC) of the change from baseline in daily average frequency of normalized daytime urinary incontinence episodes up to Week 12 was calculated for each patient in order to determine the possibility of a dose-response relationship among the 50 U, 100 U, and 200 U BOTOX doses. Table 18 presents the summary of the analysis of AUC of normalized daytime urinary incontinence episodes through Week 12. The LS mean AUC values were -1.0731, -1.0578, and -1.0465 in the 50 U, 100 U, and 200 U BOTOX groups, respectively. There were no differences between either the 100 U and 50 U group or the 200 U and 50 U group; which indicates that there was no clear dose response among the three dose groups.

Table 18. Study 191622-120 AUC of the Change From Baseline in Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes up to Week 12 (mITT)

AUC Parameters	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Differences (95% CI)[1]	200 U vs. 50 U Differences (95% CI)[1]
Mean (SD)	-0.95 (0.94)	-1.03 (1.38)	-1.43 (3.51)		
Median	-0.92	-0.78	-1.00		
LS Mean	-1.07	-1.06	-1.05	0.02 (-0.46, 0.49)	0.03 (-0.53, 0.58)

Source: Table 11-11 of study 191622-120 CSR.
[1] Least squares estimates and contrast t-test comparing specified treatment groups, are based on ANCOVA model with baseline value as covariate and treatment group, age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (≤6 or >6) and anticholinergic therapy (yes/no) at baseline as factors.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; SD, standard deviation

Durability of Response

Duration of the treatment effect was assessed by the following two secondary endpoints:

- Time between study drug injection and patient's first request for retreatment
- Time between study drug injection and qualification for retreatment

Retreatment was based on patient request, and patients qualified if at least 12 weeks had elapsed since their previous BOTOX injection, they had a total of at least two daytime urinary incontinence episodes over the 2-day diary collection period, and had not experienced a serious treatment-related adverse event at any time. Patients could request a higher dose for subsequent treatment cycles. The dose received during the retreatment was dependent on the assessment of the clinical response (efficacy and safety) to the previous blinded study treatment (50 U, 100 U, or 200 U BOTOX, not exceeding 6 U/kg). The patients remained blinded to the dose actually received upon retreatment.

Kaplan-Meier analyses of these two endpoints were conducted by the Applicant. Table 19 summarizes these analyses results. For these two endpoints, the outcomes were similar among the three BOTOX treatment groups.

Table 19. Study 191622-120 Kaplan-Meier Analyses of Time to Patient Request and Time to Qualification for Retreatment (mITT)

Parameter	BOTOX 50 U (N=38) n (%)	BOTOX 100 U (N=45) n (%)	BOTOX 200 U (N=30) n (%)
Time to request for retreatment			
n	27 (71.1)	35 (77.8)	23 (76.7)
Censored due to early drop out	5 (13.2)	4 (8.9)	4 (13.3)
Censored at last visit of the study	6 (15.8)	6 (13.3)	3 (10.0)
Median (95% CI) (Weeks)	30.6 (23.10, 39.10)	24.1 (18.10, 27.60)	29.6 (16.30, 37.30)
Time to qualification for retreatment			
n	27 (71.1)	35 (77.8)	23 (76.7)
Censored due to early drop out	5 (13.2)	4 (8.9)	4 (13.3)
Censored at last visit of the study	6 (15.8)	6 (13.3)	3 (10.0)
Median (95% CI) (Weeks)	35.0 (23.10, 39.10)	25.0 (20.00, 32.10)	29.6 (16.30, 38.00)

Source: Tables 11-12 and 11-13 of study 191622-120 CSR.
Time to request for retreatment is the time between first BOTOX injection and request for 2nd injection, regardless of fulfillment of the retreatment criteria; and n is the number of patients with events
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat

Exploratory COA (PRO) Endpoints:

As part of the exploratory analyses, the Applicant assessed two health outcomes endpoints:

- TBS – a single-item question with four scales as follows:
  - Please write down what you think about how much you leak urine (pee) now compared to how much you leaked urine (pee) **before you had any study treatment in this trial.** The four scales are: greatly improved, improved, not changed, worsened.
  - A patient was considered to have a positive treatment response if they have responded to the TBS question as either "greatly improved" or "improved."

- The PinQ is a 20-item questionnaire asking about the patient's incontinence and its consequences in daily life and relationships. Items were answered on a Likert-type scale of 0 (no) to 4 (all of the time) and a total sum score was calculated, with higher scores indicating lower health-related quality of life.

Both of the endpoints were assessed at Weeks 6 and 12, a summary of both is presented in Table 20. At the primary timepoint of Week 6:

- The proportions of patients who were deemed as "responder" based on the Applicant's definition on the TBS were 75.0% (27/36), 80.5% (33/41), and 78.6% (22/28) in the 50 U, 100 U, and 200 U BOTOX groups, respectively. The proportions in the 100 U and 200 U BOTOX groups were not statistically significantly different from the 50 U group.
- Small reductions in PinQ total scores were observed in all the three treatment groups with change from baseline scores of -2.58, -5.47, and -3.49 in the 50 U, 100 U, and 200 U BOTOX groups, respectively. The decreases in PinQ total score observed in the 100 U and 200 U BOTOX group were not statistically significantly different from the 50 U group.

Similar results were observed for both endpoints at Week 12 as well.

Table 20. Study 191622-120 Summary of Health Outcomes Endpoints

Measure Timepoint	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Difference (95% CI)	200 U vs. 50 U Difference (95% CI)
Modified Treatment Benefit Scale (TBS)					
Week 6	27/36 (75.0)	33/41 (80.5)	22/28 (78.6)	5.5 (-13.55, 25.37)	3.6 (-19.44, 25.00)
Week 12	26/34 (76.5)	34/44 (77.3)	17/27 (63.0)	0.8 (62.16, 88.53)	-13.5 (-36.81, 11.11)
PinQ					
Baseline	53.53 (19.60)	47.24 (14.77)	54.58 (16.01)		
CFB at Week 6	-2.58 (1.95)	-5.47 (1.91)	-3.49 (2.30)	-2.88 (-8.27, 2.50)	-0.90 (-6.90, 5.10)
CFB at Week 12	-4.30 (2.27)	-5.90 (2.04)	-1.33 (2.57)	-1.60 (-7.64, 4.44)	2.96 (-3.86, 9.79)

Source: Tables 11-14 and 11-15 of study 191622-120 CSR.
Abbreviations: CFB, change from baseline; CI, confidence interval; PinQ, Pediatric Incontinence Questionnaire

Integrated Review of Effectiveness

Compared to their respective baseline value, all three BOTOX treatment groups reduced the frequency of daytime urinary incontinence episodes at Weeks 2, 6, and 12. The magnitude of decrease was similar for each of the three BOTOX dose groups at the three posttreatment timepoints. At the primary timepoint of Week 6, the decrease from baseline in normalized daily average frequency of daytime urinary incontinence episodes was -1.30, -1.30, and -1.34, in the 50 U, 100 U, and 200 U BOTOX groups, respectively, with the lower bound of the 95% CI excluding 0 for each dose group. There was no statistically significant difference between the 100 U and the 50 U BOTOX groups or between the 200 U BOTOX and the 50 U BOTOX groups.

Regarding secondary endpoints, all three doses similarly improved from baseline in other clinical endpoints (urine volume at first morning catheterization, night time incontinence episodes) and urodynamic measurements. There was, however, a dose-response seen with the Applicant-defined maximum detrusor pressure during the storage phase, with the 200U dose

group having the highest proportion of patients with this measurement being <40 cmH_20, a significant urodynamic threshold to achieve.

***Statistical Reviewer Comment**: The primary efficacy endpoint did not demonstrate a statistically significant difference between the 200 U and 50 U groups and also other secondary/exploratory endpoints did not demonstrate any difference between these two groups. Without any strategy for controlling multiplicity, the findings for these two secondary endpoints are more exploratory in nature from a statistical perspective.*

***Clinical Reviewer's Comment**: Compared to their respective baseline values, all three BOTOX doses reduced the frequency of daytime urinary incontinence episodes at Week 6. The magnitude of the decrease was similar between dose groups. A reduction in PdetMax to below 40 cm H_20 is clinically meaningful in terms of preserving the upper urinary tract including renal function. A responder analysis for the proportion of patients whose PdetMax was reduced below 40 cm H_20 at Week 6 was conducted post hoc. Higher proportions of patients in the 200 U dose and 100 U dose groups had PdetMax reduced below 40 cm H_20 compared with the 50 U dose group; with the 200 U dose having the highest proportion of responders. Therefore, 200 U dose of BOTOX demonstrated an improvement in the primary endpoint and a numerical, nominally statistically significant, clinically important improvement in the secondary endpoint (PdetMax) when compared to the 50U dose group. Taken together, the evidence indicates that all three doses exerted a treatment benefit on the primary endpoint. As noted previously, this trial was designed differently from previous trials of anticholinergics which did not have a control arm. (These patients are inadequately managed by anticholinergics; therefore anticholinergics cannot serve as a control arm, nor is placebo ethically justifiable). The 50 U dose, originally thought to be a de facto placebo, was equi-effective compared with the other doses. While there were no statistical differences between the three doses, each dose resulted in statistically significant change from baseline in incontinence episodes. Therefore, we surmise that BOTOX injection was effective for the treatment of pediatric NDO and conclude that the 200U dose was the optimally effective dose given its treatment effect on maximum detrusor pressure in the storage phase.*

Additionally, pediatric patients who are less than 34 Kg in weight can be dosed at 6 U/Kg body weight. A post hoc efficacy analysis on the group of patients who received less than their assigned dose due to the 6U/kg weight cap showed similar efficacy results for the primary and select secondary endpoints to BOTOX 200 U dose.

8.2. Study 191622-121

8.2.1. Study Design

Trial Design

Study 191622-121 was a multicenter, double-blinded, long-term extension study to study 191622-120. Patients from study 191622-120 could roll over directly to study 191622-121, with

the exit visit of study 191622-120 as the entry visit (Day 1) for study 191622-121. Starting at Week 12 of study 191622-120, patients could request/qualify for retreatment and exit the study and enter into study 191622-121; or patients from study 191622-120 could enter into study 191622-121 at Week 48 of study 191622-120 if they had not yet requested/qualified for retreatment.

All patients received at least one dose of BOTOX in study 191622-121, and multiple retreatments were permitted. For the remainder of this review, Treatment 2 refers to the first dose in study 191622-121 (as Treatment 1 is the first dose received in study 191622-120), Treatment 3 refers to the second dose in study 191622-121 and so forth. Treatment was to be administered within 4 weeks of qualification for retreatment but no later than 48 weeks since enrolling in study 191622-121. This study was not a randomized study, but the dose received was blinded. The blinded dose received by each patient (50 U, 100 U, or 200 U BOTOX, not exceeding 6 U/kg) depended on the clinical response (safety, efficacy) from the randomized dose in study 191622-120.

Following a BOTOX treatment, patients had posttreatment follow-up clinic visits 2, 6, and 12, and then alternating telephone and clinic visits every 6 weeks thereafter from the time of the treatment until they qualified for further retreatment or exited the study.

The following were required for retreatment:

- Patient/parent/caregiver requests retreatment
- Patient has a total of at least 2 daytime urinary incontinence episodes over the 2-day bladder diary collection period
- At least 12 weeks has elapsed since the prior treatment dose
- Patient has not experienced a serious treatment-related adverse event at any time

Then investigators (following consultation with the patient/parent/caregiver) could have requested an increase in dose (from 50 U to 100 U, or from 100 U to 200 U) based on the patient's response to his/her previous BOTOX treatment. Those patients who had received 200 U for the previous treatment could also request a dose increase; however, the dose would remain at 200 U. If there was a second request for dose increase (after the patient received two 200 U treatments), the patient was exited from the study. Patients were also exited from the study if a dose reduction was requested by the investigator due to side effects.

Key Subject Selection Criteria

Patients in study 191622-121 had to have fulfilled the exit criteria for study 191622-120 and must not have had a treatment related serious adverse event or an adverse event in the preceding study that may indicate an unacceptable safety risk for additional BOTOX treatments, in the investigator's opinion. Patients would also be ineligible if the investigator deemed that, based on the patient's response to the treatment received in study 191622-120, a dose reduction would be warranted for a subsequent treatment. Other exclusion criteria regarding medical conditions were similar to those for study 191622-120.

Study Endpoints

In this long-term extension study no primary or secondary efficacy variables were defined. However, the Applicant defined that the key efficacy measure is the change from baseline to posttreatment in the normalized daily average frequency of daytime urinary incontinence episodes as recorded in the 2-day bladder diary during the week preceding each study visit. The study baseline frequency was defined as the daily average frequency of episodes of daytime urinary incontinence at baseline and prior to receiving BOTOX in study 191622-120.

In addition, volume of urine at first morning catheterization and the occurrence of night time urinary incontinence were efficacy measures collected using the bladder diary.

Similar to study 191622-120, as part of the exploratory analyses, the Applicant assessed two health outcomes endpoints:

- Modified TBS
- PinQ score

Urodynamic assessments were not prespecified in the study protocol; however, if an investigator deemed a urodynamic procedure was warranted following treatment, then it was performed at week 6 posttreatment. The following urodynamic efficacy measures would be included:

- MCC (mL)
- Presence or absence of an IDC
- If an IDC is present, PdetMax during the first IDC (cm H_2O)
- PdetMax during the storage phase (cm H_2O)
- DLPP (cm H_2O)

Statistical Analysis Plan

No formal statistical testing was performed in this extension study; descriptive statistics were provided together with associated t-distribution-based 95% confidence intervals for the mean change from study baseline.

Protocol Amendments

There were two protocol amendments to the original protocol (dated 14 January 2013):

- The first amendment was dated 4 October 2013. The main change was to provide clarifications and guidance to investigators regarding entry criteria, assignment to treatment group for analysis purposes, study procedures, and concomitant medications/procedures. There were also a few procedures added to the protocol which included addition of renal function assessment (eGFR), and form for collecting “Reason for Requesting Retreatment” at Week 12 and later.

- The second amendment was dated 5 May 2016. The main change was to lower the minimum age to 5 years old from 8 years old and to include dosing information for a younger patient population. The amendment clarified that study baseline refers to information collected at the start of study 191622-120.

Compliance With Good Clinical Practices

The Applicant attested to compliance with good clinical practice for the two studies in accordance with the ICH guidelines and with 21 CFR parts 50, 56, and 312.

Data Quality and Integrity

The submission contains all required components of the 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.

Financial Disclosure

Financial disclosure was made for all required studies submitted to this application. There is no evidence to suggest that a financial relationship had any impact on study results.

8.2.2. Study Results

Patient Disposition

Of the 100 patients who completed study 191622-120, 95 enrolled into study 191622-121 and 90 of these patients received at least 1 BOTOX treatment in study 191622-121. At the end of this extension study, the Applicant reported that 75 patients completed and 20 had discontinued early. Table 21 presents the patient disposition for study 191622-121. Overall, of the 20 (21.1%) patients who discontinued from the study early, most (9/95; 9.5%) discontinued due to "other" reasons. The 200 U group had more patients withdraw due to "other" reasons.

Table 21. Study 191622-121 Patient Disposition

Disposition	BOTOX 50U n (%)	BOTOX 100U n (%)	BOTOX 200U n (%)	Total n (%)
Completed study 191622-120	33	41	26	100
Enrolled in study 191622-121	31 (100.0)	39 (100.0)	25 (100.0)	95 (100.0)
Treated	28 (90.3)	38 (97.4)	24 (96.0)	90 (94.7)
Completed study	22 (71.0)	36 (92.3)	17 (68.0)	75 (78.9)
Discontinued	9 (29.0)	3 (7.7)	8 (32.0)	20 (21.1)
Reason for discontinuation				
Adverse event	1 (3.2)	0	0	1 (1.1)
Lack of efficacy	1 (3.2)	0	1 (4.0)	2 (2.1)
Withdrawal by subject	3 (9.7)	1 (2.6)	1 (4.0)	5 (5.3)
Protocol deviation	1 (3.2)	0	0	1 (1.1)
Other	1 (3.2)	2 (5.1)	6 (2.4)	9 (9.5)

Source: Table 10-1 of study 191622-121 Report.

Across both Studies 191622-120 and 191622-121, 90 patients received 2 treatments (Treatment 1 in study 191622-120, Treatment 2 in study 191622-121), 55 patients received 3 treatments (Treatment 1 in study 191622-120, Treatments 2 and 3 in study 191622-121), and 11 patients received 4 treatments (Treatment 1 in study 191622-120, and Treatments 2, 3, and 4 in study 191622-121). In study 191622-121, patients did not necessarily continue with their randomized dose from study 191622-120 or with the same dose from one treatment to the next. In study 191622-121, investigators could have requested an increase in dose (from 50 U to 100 U, or from 100 U to 200 U) based on the patient's response to his/her previous BOTOX treatment:

- Of the 31 patients who received Treatment 1 with 50 U BOTOX, the dose was increased to 100 U for 19 patients (61.3%) for Treatment 2; from Treatment 2 to Treatment 3, the dose was increased from 50 U to 100 U for 1 patient; there was no dose increase for patients in the 50 U group to 100 U from Treatment 3 to Treatment 4.
- Of the 39 patients who received Treatment 1 with 100 U BOTOX, a total of 16 patients (41.0%) requested a dose increase. Twelve of these 16 patients had a dose increase to 200 U BOTOX with Treatment 2 (four patients remained in the 100 U group due to the 6 U/kg cap); from Treatment 2 to Treatment 3, seven patients had a dose increase from 100 U to 200 U; no patients in the 100 U group had a dose increase to 200 U from Treatment 3 to Treatment 4.
- Of the 25 patients who received Treatment 1 with 200 U BOTOX, 16 (64.0%) requested a dose increase but remained on 200 U for Treatment 2 per protocol. Five patients requested a second increase in dose at the end of Treatment Cycle 2 and thus were exited from the study. Two patients (not initially allocated to the 200 U group) requested an increase in dose to 200 U at the end of Treatment Cycle 3 and received 200 U in Treatment Cycle 4.

Table 22 presents number of patients treated for each Treatment Number.

Table 22. Study 191622-121 Patients Treated by Treatment Number*

Treatment Number	BOTOX 50U n	BOTOX 100U n	BOTOX 200U n	Total N
1	31	39	25	95
2	9	45	36	90
3	5	16	34	55
4	3	4	4	11

Source: Statistical Reviewer's Summary.
*Treatment 1 is from study 191622-120, the remaining Treatments 2-4 are from study 191622-121.

Protocol Violations/Deviations

The most commonly reported protocol deviations were:

- As in study 191622-120, 11/95 (11.5%) of patients had no record of being previously inadequately managed with one or more anticholinergic agents for the treatment of NDO.
- Significant deviation in patient diary completion, mostly due to missing or no bladder diary at the qualification visit, the bladder diary not having been completed at the Week

6 visit, or because the patient was recorded as qualified for retreatment but did not meet the retreatment criterion for at least 2 daytime urinary incontinence episodes over the 2-day diary collection period, (8/95, 8.4%)

- Significant deficiency in consent process, mostly due to the assent form not being signed, being signed late, or only 1 of the parents signing the parental consent (5/95, 5.3%)
- Patient received a different treatment than assigned, mostly due to reconstitution errors (4/95, 4.2%). See Treatment Compliance section below for details.

One patient (Patient (b) (6)) requested retreatment based on night time incontinence and was inadvertently not recorded as a protocol deviation.

Reviewer comment: *These protocol deviations did not alter the safety and efficacy findings of the study.*

Demographic Characteristics

Demographic and baseline characteristics were summarized for the 95 patients that rolled over from study 191622-120. As expected, the demographics are similar to those of study 191622-120: most study patients were White (over 70%); there were slightly more male (53.7%) patients than female patients; and the mean age of the study was approximately 11 years old. Overall, there were similar percentage of patients (approximately 50%) in both the <12 years old group and ≥12 years old group but there was a slightly higher proportion of older patients (≥12 years) in the 200 U BOTOX group compared to the 50 U and 100 U BOTOX groups (60.0% versus 51.6% and 43.6%, respectively).

Table 23. Study 191622-121 Demographic Characteristics

Demographic Parameters	BOTOX 50U (N=31) n (%)	BOTOX 100U (N=39) n (%)	BOTOX 200U (N=25) n (%)	Total (N=95) n (%)
Sex				
Male	14 (45.2)	25 (64.1)	12 (48.0)	51 (53.7)
Female	17 (54.8)	14 (35.9)	13 (52.0)	44 (46.3)
Age				
Mean years (SD)	11.7 (3.50)	10.8 (3.36)	11.7 (3.22)	11.3 (3.36)
Median (years)	12	11	12	12
Min, max (years)	5.0, 17.0	5.0, 16.0	6.0, 17.0	5.0, 17.0
Age group				
<12 years	15 (48.4)	22 (56.4)	10 (40.0)	47 (49.5)
≥12 years	16 (51.6)	17 (43.6)	15 (60.0)	48 (50.5)
Race				
White	22 (71.0)	28 (71.8)	18 (72.0)	68 (71.6)
Black or African American	6 (19.4)	3 (7.7)	2 (8.0)	11 (11.6)
Asian	1 (3.2)	2 (5.1)	0	3 (3.2)
Hispanic	1 (3.2)	3 (7.7)	3 (12.0)	7 (7.4)
Other[1]	1 (3.2)	3 (7.7)	2 (8.0)	6 (6.3)
Weight (kg)				
Mean (SD)	43.42 (18.28)	40.90 (24.64)	45.51 (16.14)	42.96 (20.50)
Median	42.00	32.70	45.00	41.85
Min, max	16.9, 87.7	15.8, 127.9	27.6, 109.8	15.8, 127.9

Demographic Parameters	BOTOX 50U (N=31) n (%)	BOTOX 100U (N=39) n (%)	BOTOX 200U (N=25) n (%)	Total (N=95) n (%)
Height (cm)				
Mean (SD)	138.95 (19.91)	134.89 (21.60)	143.45 (15.59)	138.48 (19.72)
Median	134.62	134.50	146.00	138.50
Min, max	105.1, 175.0	95.0, 174.0	116.3, 170.0	95.0, 175.0

Source: Table 10-5 of study 191622-121 CSR.
Abbreviations: SD, standard deviation

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

Other baseline disease characteristics for study 191622-121 are presented in Table 24. Note that these baseline values are those obtained at baseline and prior to BOTOX treatment in study 191622-120.

Table 24. Study 191622-121 Other Baseline Characteristics

Characteristics	BOTOX 50U (N=38)	BOTOX 100U (N=45)	BOTOX 200U (N=30)	Total (N=113)
Stratification, n (%)				
Age <12 years, daytime UI ≤6	7 (22.6)	16 (41.0)	7 (28.0)	30 (31.6)
Age <12 years, daytime UI >6	8 (25.8)	6 (15.4)	3 (12.0)	17 (17.9)
Age ≥12 years, daytime UI ≤6	11 (35.5)	8 (20.5)	7 (28.0)	26 (27.4)
Age ≥12 years, daytime UI >6	0 (0.0)	0 (0.0)	2 (8.0)	2 (2.1)
Neurologic characteristics, n (%)				
Spinal dysraphism	26 (83.9)	33 (84.6)	23 (92.0)	82 (86.3)
Spinal cord injury	5 (16.1)	6 (15.4)	2 (8.0)	13 (13.7)
Transverse myelitis	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)
Anticholinergic therapy at baseline, n (%)				
Yes	20 (64.5)	20 (51.3)	9 (32.0)	48 (50.5)
No	11 (35.3)	19 (48.7)	17 (68.0)	47 (49.5)
Daily average frequency of daytime UI episodes[1]				
Mean (SD)	2.66 (0.88)	2.97 (1.14)	4.10 (5.72)	3.15 (2.99)
Median	2.60	2.80	2.70	2.70
Min, max	0.8, 4.6	1.3, 6.1	1.4, 29.5	0.8, 29.5
n	31	39	23	93
Urine volume at first morning catheterization (mL)				
Mean (SD)	221.18 (176.55)	164.20 (122.22)	171.82 (121.56)	185.45 (143.72)
Median	155.00	122.50	167.50	150.00
Min, max	25.0, 725.0	24.5, 465.0	7.5, 450.0	7.5, 725.0
n	31	38	22	91
Night time urinary incontinence, n (%)				
Yes	31 (100.0)	33 (84.6)	22 (88.0)	86 (90.5)
No	0 (0.0)	6 (15.4)	1 (4.0)	7 (7.4)
Missing	0 (0.0)	0 (0.0)	2 (8.0)	2 (2.1)
MCC (mL)				
Mean (SD)	185.13 (108.56)	176.55 (137.04)	203.82 (131.30)	186.08 (125.83)
Median	169.00	125.50	155.00	151.00
Min, max	32.0, 500.0	33.0, 643.0	34.0, 500.0	32.0, 643.0
n	30	38	22	90

Characteristics	BOTOX 50U (N=38)	BOTOX 100U (N=45)	BOTOX 200U (N=30)	Total (N=113)
PdetMax1stIDC (cm H2O) (if IDC present)				
Mean (SD)	33.96 (29.28)	31.61 (27.36)	20.85 (14.23)	29.71 (25.72)
Median	26.00	21.00	15.00	20.00
Min, max	5.0, 103.0	7.0, 128.0	7.0, 59.0	5.0, 128.0
n	27	33	20	80

Source: Table 10-6 of study 191622-121 CSR.
[1] Normalized to a 12-hour period
Abbreviations: MCC, maximum cystometric capacity; PdetMax, maximum detrusor pressure; PdetMax1stIDC, PdetMax during the first IDC; SD, standard deviation; UTI, urinary tract infection

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Among the 95 patients who received BOTOX, ten (10) did not receive the injection per protocol during any of the Treatment Cycles (1 to 4). Eight (8) of the 10 patients were injected in locations other than, or in addition to, the location specified by the injection paradigm in the protocol; two (2) of the 8 also received fewer than the 10 injections specified in the protocol.

The Applicant reported that the majority of treatment assignments were performed correctly, in compliance with the study protocol. However, five patients received an incorrect treatment assignment due to reconstitution errors:

- In Treatment 1 (study 191622-120): due to the 6 U/kg cap, one patient (Patient (b) (6) should have received 180 U but actually received 200 U BOTOX.
- In Treatment 2:
  - One patient (Patient (b) (6) should have received 200 U BOTOX but received 100 U
  - One patient (Patient should have received 200 U BOTOX but received 156 U
- In Treatment 3:
  - One patient (Patient (b) (6) should have received 200 U BOTOX but received 144 U
  - One patient (Patient should have received 200 U BOTOX but received 192 U
- In Treatment 4: One patient (Patient (b) (6)) should have received 200 U BOTOX but received 144 U

Of the 95 patients who rolled over into study 191622-121, anticholinergic therapy had been used by 85 patients (89.5%) prior to enrolling in study 191622-120. 84/95 were recorded as being inadequately managed on that medication. The Applicant reported that 11 patients did not have prior anticholinergic use recorded. During study 191622-121, patients who were receiving anticholinergic medication at baseline (50.5% of total enrolled) were permitted to continue taking their anticholinergic medication throughout the study at a stable dose, or modify the dosage, or discontinue their use. The use of other medications or therapies (other than anticholinergics) to treat the symptoms of NDO within 7 days of the start of the screening period procedures and during the study was prohibited. At baseline, use of anticholinergic therapy was recorded for 52.6% (50/95) of patients; anticholinergic use at baseline was lower in the 200 U BOTOX group (9/25, 36.0%). The Applicant further reported that during the study, the most commonly used classes of medications other than anticholinergic therapies were anilides (63.2% of patients), first generation cephalosporins (54.7%), opioid anesthetics (54.7%), other general anesthetics (52.6%), and benzodiazepine derivatives, (52.6%).

All patients received prophylactic antibiotics prior to each treatment administration. Anesthesia was used for all patients during the treatment administration. Children <12 years old were administered general anesthesia and children 12 to 17 years old could request local anesthesia instead of general anesthesia.

Efficacy Results – Key Efficacy Endpoint

The key efficacy endpoint for study 191622-121 was the mean change from study baseline for the daily average frequency of normalized daytime urinary incontinence episodes at Week 6 of each treatment cycle. It should be noted that Cycle 1 was the preceding study 191622-120; the extension study (study 191622-121) started from Cycle 2.

All three doses resulted in a reduction from baseline in day time urinary incontinence episodes. These reductions were similar to those seen with Treatment Cycle 1. The mean reduction of daytime urinary incontinence episodes at Week 6 was similar among the three dose groups post second treatment (Cycle 2) (-1.07, -1.70, and -1.64, in the 50 U, 100 U, and 200 U BOTOX groups, respectively); and was also similar post the third treatment (Cycle 3) (-1.92, -1.73, and -2.74, in the 50 U, 100 U, and 200 U BOTOX groups, respectively) with a slightly higher numerical difference for 200 U BOTOX dose in cycle 3 and 4.

Table 25. Study 191622-121 Summary of Daytime Average Frequency of Urinary Incontinence Episodes at Week 6 (Cycle 2 to Cycle 4)

Treatment Cycle Parameter	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)
Cycle 2			
n	9	45	36
Baseline (SD)	2.57 (0.94)	2.80 (0.92)	3.83 (4.62)
Change from baseline at Week 6 (SD)	-1.07 (2.09)	-1.70 (1.33)	-1.64 (1.91)
(95% CI)	(-3.3, 1.1)	(-4.2, 1.5)	(-6.8, 1.1)
Cycle 3			
n	5	16	34
Baseline (SD)	2.48 (0.23)	2.94 (0.92)	3.80 (4.68)
Change from baseline at Week 6 (SD)	-1.92 (0.86)	-1.73 (1.06)	-2.74 (4.83)
(95% CI)	(-3.0, -0.9)	(-2.3, -1.2)	(-4.5, -1.0)
Cycle 4			
n	3	4	4
Baseline (SD)	2.53 (0.31)	9.3 (13.48)	3.80 (1.46)
Change from baseline at Week 6 (SD)	-1.53 (0.42)	-8.85 (13.77)	-2.80 (2.46)

Source: Table 11-1 of study 191622-121 CSR.
[1] Least squares estimate and contrast t-test comparing specified treatment groups, are based on ANCOVA model with baseline value as covariate and treatment group, age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (≤6 or >6) and anticholinergic therapy (yes/no) at baseline as factors.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; SD, standard deviation

Integrated Review of Effectiveness

Compared to Treatment Cycle 1 study 191622-121, Treatment Cycles 2 and 3 in study 191622-120, had similar magnitude of reduction from baseline for the frequency of daytime urinary

incontinence episodes at Week 6. Note that by Treatment Cycle 4, there were too few patients left for any meaningful interpretation of the data.

In addition, for the following additional endpoints collected by the Applicant, all three BOTOX treatment groups had similar outcomes during Treatment Cycles 2 and 3 as well:

- Urine volume at first morning catheterization
- Presence/absence of night time urinary incontinence
- Time between study drug injection and patient's first request for retreatment
- Time between study drug injection and qualification for retreatment
- Modified TBS
- PinQ

8.3. Assessment of Efficacy Across Trials

The efficacy of three doses (50 U, 100 U, and 200 U) of BOTOX in patients with urinary incontinence due to NDO who were 5 to 17 years of age and who had not been adequately managed with anticholinergic therapy has been evaluated in two studies: Studies 191622-120 and 191622-121. Study 191622-120 was a Phase 3 randomized study designed to assessing the safety and efficacy of BOTOX for the treatment of urinary incontinence due to NDO in pediatric patients; study 191622-120 did not have a placebo arm but a lower dose of 50 U was included since this dose was anticipated to be "sub-therapeutic." As an extension study to study 191622-120, study 191622-121 was not a randomized study and focused more on long-term data over repeated treatments.

In order to demonstrate treatment effects over time, the following summary of efficacy endpoints put results of both Studies 191622-120 and 191622-121 together. Please note that Treatment Cycle 1 refers to data from study 191622-120; and Treatment Cycles 2 to 4 refer to data in the long-term extension study 191622-121. In study 191622-121, patients could request a dose increase for retreatment, treatment dose was not randomized but remained blinded, and all efficacy analyses were based on the dose group (50U, 100U, or 200U) that most closely approximated the treatment dose actually received in each treatment cycle. It is also noted as the treatment cycle increased, number of patients in lower dose groups decreased as some patients shifted to higher dose group. By Treatment Cycle 4, there were too few patients left for any meaningful interpretation of the data.

Primary Efficacy Endpoint/Key Efficacy Endpoint

The change from baseline to posttreatment in the normalized daily average frequency of daytime urinary incontinence episodes was the primary efficacy variable for study 191622-120 and the key efficacy variable for the extension study 191622-121. This variable was measured at Weeks 2, 6, and 12 of each treatment cycle, with Week 6 as the primary timepoint. It is noted that daytime urinary incontinence episodes at study baseline was higher in the 200 U BOTOX group (3.68) than the 50 U and 100 U BOTOX groups (2.81 and 2.99, respectively). This is due to 1 patient (Patient 1005) in the 200 U group who had an excessively high frequency of average

daytime urinary incontinence episodes at baseline (29.5 daytime urinary incontinence episodes), while all other patients had less than 7 episodes. The results presented in the following Table 26 excluded this one subject from the analysis to minimize the bias introduced by this one outlier. Note that by Treatment Cycle 4, there were too few patients left for any meaningful interpretation of the data. All three BOTOX doses reduced from baseline in day time incontinence episodes; the magnitude in reduction was similar across the 3 dose groups. There was no difference in the treatment effect for the dose groups.

Table 26. Summary of Daily Normalized Daytime Average Frequency of Urinary Incontinence Episodes by Treatment Cycle

Treatment Cycle Timepoint	BOTOX 50 U (N=38)	BOTOX 100 U (N=45)	BOTOX 200 U (N=30)	100 U vs. 50 U Differences (95% CI)[1]	200 U vs. 50 U Differences (95% CI)[1]
Cycle 1					
n	38	45	30		
Baseline	2.81 (1.05)	2.99 (1.07)	2.79 (1.39)		
Week 2[1]	-1.08	0.83	-1.06	0.25 (-0.33, 0.83)	0.03 (-0.65, 0.70)
Week 6[1]	-1.08	-1.10	-1.10	-0.02 (-0.57, 0.52)	-0.02 (-0.65, 0.62)
Week 12[1]	-0.95	-1.24	-0.70	-0.29 (-0.88, 0.30)	0.25 (-0.44, 0.93)
Cycle 2					
n	9	45	35		
Baseline	2.57 (0.94)	2.80 (0.92)	3.10 (1.44)		
Week 2	-1.61 (0.65)	-1.64 (1.34)	-1.67 (1.96)	0.21 (-0.79, 1.22)	0.29 (-0.73, 1.32)
Week 6	-1.07 (2.09)	-1.70 (1.33)	-1.64 (1.91)	-0.33 (-1.50, 0.83)	-0.08 (-1.26, 1.11)
Week 12	-0.83 (1.27)	-1.23 (1.24)	-1.21 (2.01)	-0.31 (-1.31, 0.70)	-0.16 (-1.20, 0.87)
Cycle 3					
n	5	16	33		
Baseline	2.48 (0.23)	2.94 (0.92)	3.02 (1.14)		
Week 2	-1.82 (0.75)	-1.77 (1.18)	-1.88 (1.09)	0.32 (-0.78, 1.43)	0.17 (-0.87, 1.21)
Week 6	-1.92 (0.86)	-1.73 (1.06)	-1.93 (1.30)	0.32 (-0.82, 1.47)	0.12 (-0.96, 1.20)
Week 12	-1.84 (0.74)	-1.57 (1.03)	-1.86 (1.52)	0.60 (-0.65, 1.84)	0.20 (-0.99, 1.39)
Cycle 4					
n	3	4	4		
Week 2	2.53 (0.31)	9.3 (13.48)	3.80 (1.46)		
Week 6	-1.47 (0.60)	-8.50 (13.67)	-2.85 (1.90)		
Week 12	-1.53 (0.42)	-8.85 (13.77)	-2.80 (2.46)		
Week 2	-0.40 (1.48)	-8.93 (13.72)	-2.35 (2.99)		

Source: Statistical Reviewer's Analysis excluding one baseline outlier.
[1] Least squares estimate and contrast t-test comparing specified treatment groups, are based on ANCOVA model with baseline value as covariate and treatment group, age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (≤6 or >6) and anticholinergic therapy (yes/no) at baseline as factors.
Abbreviations: CI, confidence interval

Subpopulations

The effect of BOTOX in population subgroups has not shown any difference across gender, age group (<12 versus 12 to 17 years old), race, sex, baseline day time urinary incontinence episodes (≤6 versus >6), concomitant anticholinergic use in both studies 191622-120 and 191622-121. Post hoc subgroup analyses of efficacy in study 191622-120 for geographic region (North America versus European Union) and etiology (spinal dysraphism versus spinal cord injury) did not show any differences.

Additional Efficacy Considerations

Other than PdetMax (cm H_2O) during the storage phase which showed clinical improvement with 200 U BOTOX compared with the 50 U BOTOX at Week 6 in Treatment Cycle 1, with the improvement appearing to be dose-related, all the three BOTOX treatment groups had similar outcomes at each treatment cycle for the following secondary and exploratory endpoints:

- Urine volume at first morning catheterization (mL)
- Presence or absence of night time urinary incontinence
- Presence/absence of an IDC
- If an IDC is present, PdetMax during the first IDC (cm H_2O)
- MCC
- PdetMax (cm H_2O) during the Storage Phase
- If a leak occurs, DLPP
- Time between study drug injection and patient's first request for retreatment
- Time between study drug injection and qualification for retreatment
- Modified TBS
- PinQ

8.4. Integrated Assessment of Effectiveness

Based on the totality of evidence, BOTOX at the three doses evaluated (50 U, 100 U, and 200 U) improved from baseline both clinical and urodynamic endpoints in NDO children inadequately managed with first-line treatment with anticholinergic medications; the lower bound of the 95% confidence interval for the primary endpoint of daytime urinary incontinence episodes for each dose excluded zero. The treatment effects were durable, with the mean time to request for retreatment to be at approximately 6 months. Further, the drug effects on clinical outcomes were sustained with repeated treatments of BOTOX injection. Based on the prespecified statistical analyses, the higher doses (200 U, 100 U) were not statistically different than the lower dose of 50 U, indicating that the higher doses did not provide additional benefits compared to the 50 U dose. However, the 200 U dose appeared to be the optimal effective dose based on a dose-response seen on the maximal detrusor pressure and proportion of "responders." This latter measurement is clinically prognostic for upper urinary tract deterioration. Based on protocol-specified dose cap of 6 U/kg, there will be children with lower body weigh who would not be eligible for the 200 U. Post hoc analyses in these children suggest that the efficacy findings were similar to the 200 U dose group. From an efficacy perspective, the clinical team recommends approval of the 200 U for children weighing at least 34 kilograms, and 6 U/kg for children weighing less than 34 kilograms.

8.5. Review of Safety

8.5.1. Safety Review Approach

The safety review was based on data from studies 191622-120 and 191622-121. The safety population includes all patients who received the study drug and safety analyses are based on actual treatment received. The reviewer focused primarily on data obtained during the 12 weeks immediately following the first injection of study drug in study 191622-120. Data from the extension study 191622-121 were reviewed for deaths and any safety signals identified in study 191622-120. Data were pooled across studies for exposure only. Data from all patients study 191622-120 (n=113) were pooled with the final data analysis from patients that participated in the long-term extension study 191622-121 (n=95). All other analyses were based on data from the randomized study 191622-120 only.

The reviewer also verified the Applicant's post hoc analyses for:

1. Duration of exposure to study treatment
2. Summary of type of anesthesia received during study drug administration
3. Summary of AE by subgroups:
   a. Age: <12 versus ≥12
   b. Gender: male versus female
   c. Race: Caucasian versus non-Caucasian
   d. Geographic region (North America versus European Union)
   e. Type of anesthesia received (general anesthesia versus no general anesthesia)
   f. Anticholinergic use at baseline (yes versus no)
   g. Etiology (spinal dysraphism versus spinal cord injury)
4. AE listing for participants who received a dose less than assigned due to the 6 U/kg dose cap

8.5.2. Review of the Safety Database

Overall Exposure

The safety population is comprised of the 113 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, due to the 6 U/kg weight cap), the patient was reassigned to the dose group closest to the actual dose received. Of the 113 patients who received at least one dose, 107 received treatment dose on Day 1 as randomized, while five patients randomized to the 200 U group were assigned to the 100 U group and 1 randomized to the 200 U group was assigned to the 50 U group, due to the weight-based dose cap.

Table 27. Participant Exposure by Number of Treatments Received, Safety Population

Treatment Sequence	Total (N=113) n (%)
BOTOX 50U	10 (8.8)
BOTOX 50U-BOTOX 50U	3 (2.7)
BOTOX 50U-BOTOX 100U	7 (6.2)
BOTOX 50U-BOTOX 50U-BOTOX 50U	2 (1.8)
BOTOX 50U-BOTOX 50U-BOTOX 100U	1 (0.9)
BOTOX 50U-BOTOX 100U-BOTOX 100U	5 (4.4)
BOTOX 50U-BOTOX 100U-BOTOX 200U	5 (4.4)
BOTOX 50U-BOTOX 50U-BOTOX 50U-BOTOX 50U	3 (2.7)
BOTOX 50U-BOTOX 100U-BOTOX 100U-BOTOX 100U	1 (0.9)
BOTOX 50U-BOTOX 100U-BOTOX 200U-BOTOX 200U	1 (0.9)
BOTOX 100U	7 (6.2)
BOTOX 100U-BOTOX 100U	9 (8.0)
BOTOX 100U-BOTOX 200U	3 (2.7)
BOTOX 100U-BOTOX 100U-BOTOX 100U	7 (6.2)
BOTOX 100U-BOTOX 100U-BOTOX 200U	8 (7.1)
BOTOX 100U-BOTOX 200U-BOTOX 200U	8 (7.1)
BOTOX 100U-BOTOX 100U-BOTOX 100U-BOTOX 100U	2 (1.8)
BOTOX 100U-BOTOX 200U-BOTOX 200U-BOTOX 200U	1 (0.9)
BOTOX 200U	6 (5.3)
BOTOX 200U-BOTOX 200U	13 (11.5)
BOTOX 200U-BOTOX 200U-BOTOX 200U	8 (7.1)
BOTOX 200U-BOTOX 200U-BOTOX 200U-BOTOX 100U [1]	1 (0.9)
BOTOX 200U-BOTOX 200U-BOTOX 200U-BOTOX 200U	2 (1.8)

Data from all participants in Study 191622-120 (n=113) are pooled with the data from all participants in the long-term extension
Study 191622-121 (n=95). Treatment Group used for analysis is based on actual BOTOX dose unit received: participants that received
< 75 U are in the 50 U group, >= 75 U to < 150 U are in the 100 U group; >150 U to 200 U are in the 200 U group.
[1] Patient was assigned 200 U but received 100 U due to a site error.
Source: ISS, Table 1-2.1

Adapted from The Integrated Summary of Safety Table 1-2.2 (p12/55)

Table 27 demonstrates that few patients continued in the 50 U dose group for multiple cycles; patients requested and received a higher dose. Of the initial 113 patients, only 11 received four treatments.

Cumulatively, the duration of exposure showed no trends by dose group. The mean duration of exposure to the 50 U dose was 56.6 weeks; to the 100 U dose, 51.6 weeks; and to the 200 U dose, 48.8 weeks.

Table 28. Cumulative Duration of Study Drug Exposure, Safety Population

Duration of Exposure (weeks)	BOTOX 50U (N=38)	BOTOX 100U (N=66)	BOTOX 200U (N=56)
>= 2 weeks	38 (100.0%)	66 (100.0%)	56 (100.0%)
>= 6 weeks	37 (97.4%)	66 (100.0%)	56 (100.0%)
>= 12 weeks	36 (94.7%)	66 (100.0%)	53 (94.6%)
>= 18 weeks	29 (76.3%)	54 (81.8%)	45 (80.4%)
>= 24 weeks	24 (63.2%)	49 (74.2%)	42 (75.0%)
>= 30 weeks	21 (55.3%)	46 (69.7%)	38 (67.9%)
>= 36 weeks	19 (50.0%)	45 (68.2%)	35 (62.5%)
>= 42 weeks	16 (42.1%)	43 (65.2%)	30 (53.6%)
>= 48 weeks	14 (36.8%)	36 (54.5%)	27 (48.2%)
>= 54 weeks	12 (31.6%)	29 (43.9%)	20 (35.7%)
>= 60 weeks	11 (28.9%)	25 (37.9%)	18 (32.1%)
>= 66 weeks	11 (28.9%)	20 (30.3%)	15 (26.8%)
>= 72 weeks	11 (28.9%)	18 (27.3%)	14 (25.0%)
>= 78 weeks	11 (28.9%)	15 (22.7%)	14 (25.0%)
>= 84 weeks	10 (26.3%)	12 (18.2%)	12 (21.4%)
>= 90 weeks	9 (23.7%)	8 (12.1%)	8 (14.3%)
>= 96 weeks	6 (15.8%)	3 (4.5%)	4 (7.1%)
n	38	66	56
Mean (SD)	46.6 (33.56)	51.6 (27.67)	48.8 (29.28)
Median	36.0	49.4	46.1
Q1, Q3	(18.0, 86.4)	(23.1, 75.0)	(24.5, 74.3)
Min, Max	(5.4, 105.7)	(12.0, 107.4)	(11.4, 105.3)

Source: Integrated Summary of Safety submission Table 1-2.3 (p.13.50)

Adequacy of the Safety Database

The safety database is adequate for evaluation and aligns with advice in interactions with the Division during protocol development.

8.5.3. Adequacy of Applicant's Clinical Safety Assessments

The Applicant's clinical safety assessments were adequate and aligned with advice from Agency interactions during protocol development.

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.

Twelve study sites were closed due to difficulties with recruitment, prior to screening any patients. Three sites closed after some patients were screened but before they were randomized. Nine sites requested closure after randomization and enrollment of patients, four due to difficulty with recruitment and the volume of study paperwork, one due to loos of study coordinator, one because their standard practice was not in line with the study protocol, one closed after database lock for study 191622-120, and one (10013) due to issue with protocol adherence and GCP compliance.

Categorization of Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 21.0) and described using the preferred term. For the two studies, the Applicant presented adverse events in two ways: events occurring within the entire Treatment Cycle (from the time of Treatment injection to time of retreatment or exit from the study) and events occurring within the first 12 weeks after BOTOX administration, in order to capture the AE profile within a cycle

(since cycle length may vary) and also within a standardized time frame/exposure period in each cycle, respectively.

The Applicant captured by cycle:

- All treatment-emergent adverse events (TEAEs)
- Treatment-related TEAEs which were defined as AEs related to the study drug or injection procedure or both
- Study drug-related TEAEs
- Study injection related TEAEs
- All STEAEs
- Treatment-related STEAEs
- TEAES leading to discontinuation

For the purposes of this review, the clinical reviewer reviewed all events as presented, but chose to present the events occurring within each entire treatment cycle, as it represents what could occur in real-world use.

The protocol-defined specific adverse events are as follows:

- UTI: a symptomatic UTI that requires treatment in the opinion of the investigator.
- Urinary Retention: Reported only in patients who had the ability to void spontaneously between catheterizations prior to study treatment. The event was defined as the inability to spontaneously void for at least 24 hours, not in conjunction with constipation. (Patients in the study did CIC as a mainstay of managing their NDO, so this was not relevant to this population as in the adult NDO population.)

Routine Clinical Tests

Routine clinical tests for safety included:

- Physical examination at screening, retreatment and exit: general appearance; head, eyes, ears, nose, throat examination; heart/cardiovascular; lungs; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; skin; genitourinary; and other findings;
- Weight and height at screening, retreatment and exit
- Vital signs at each study clinic visit and prior to any invasive procedures: heart rate, blood pressure, respiration rate, and body temperature); urinalysis (with urine culture/sensitivity, as applicable.
- Urinalysis, urine culture and sensitivity: urinalysis was performed at screening, 2, 6, and 12 weeks and at retreatment. If there were findings suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or white blood cells (WBCs), red blood cells and/or bacteria), then urine culture and sensitivity were performed. Only central lab results were used in the safety analysis.
- Hematology: was assessed on day 1 prior to randomization/treatment if a patient was not getting general anesthesia, or with intravenous line placement on Day 1 prior to

treatment if the patient was getting general anesthesia. Also obtained at week 12, study exit.

- Clinical chemistry: was assessed on day 1 prior to randomization/treatment if a patient was not getting general anesthesia, or with intravenous line placement on Day 1 prior to treatment if the patient was getting general anesthesia. Also checked at week 12, study exit. Included a basic metabolic panel as well as liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin), total protein, calcium, magnesium, phosphorus, and uric acid.
- Renal function testing: estimate of the glomerular filtration rate (eGFR); on day of randomization/day 1 prior to treatment, week 12 and study exit.
- Immunogenicity testing: collected on day 1 prior to treatment, at week 12 and study exit.
- Kidney and bladder ultrasound at screening, retreatment and exit. If there were unclear new findings suggestive of stones (kidney, ureter, or bladder), other diagnostic measures were performed including x-ray with or without contrast, urogram, computed tomography scan, magnetic resonance imaging, or cystoscopy.
- Urine pregnancy test for females who are postmenarche.

8.5.4. Safety Results

Deaths

There were no deaths reported during the study.

Serious Adverse Events

Serious treatment-emergent adverse events (STEAEs) were reported in 9/113 (8.0%) of patients in study 191622-120. There was no difference in STEAEs by dose group: (10.5% [4/38], 6.7% [3/45]), and 6.7% [2/30] in the 50 U, 100 U, and 200 U BOTOX groups, respectively). Most were assessed as being unrelated to study treatment; however, one UTI was assessed as being related to study drug administration (Patient (b) (6)). This reviewer finds that two more UTI STEAEs (Patient (b) (6) and Patient (b) (6)) were possibly related to study treatment. In study 190622-121, the frequency of STEAEs was 12.2% in Treatment Cycle 2 and 5.5% in Treatment Cycle 3. Again, the Applicant considered two UTIs related to study drug administration (Patient (b) (6) and Patient (b) (6)). This reviewer actually reclassified the UTI event in Patient (b) (6) as pyelonephritis. The narratives for UTIs that were considered serious adverse events are included below in Section 8.5.5.1 and those for pyelonephritis are included below in Section 8.5.5.6.

Serious adverse event (SAE) narratives were provided for the following cases:

Table 29. SAE Narratives and Location in Review

Patient ID	SAE	Assessed as Related or Not by Investigator?	Narrative Location in this Review
Study 190622-120			
(b) (6)	Epididymitis, orchitis	Not related	Section 8.5.4
	Arteriovenous fistula thrombosis	Not related	Section 8.5.4
	Postoperative wound infection	Not related	Section 8.5.4
	Viral encephalitis, hydrocephalus	Not related	Section 8.5.4
	Hypertension	Not related	Section 8.5.4 below under "Vital Signs"
	UTI	Not related	Sections 8.5.5.1 and 8.5.5.6
	UTI	Not related	Section 8.5.5.1
	UTI	Related	Section 8.5.5.1
	UTI	Not related	Section 8.5.5.1
	PDSOT	Not related	Section 8.5.5.7
	PDSOT	Not related	Section 8.5.5.7
Study 191622-121			
(b) (6)	Pneumonia	Not related	Section 8.5.4
	Foot deformity	Not related	Section 8.5.4
	Wound infection	Not related	Section 8.5.4
	Fistula	Not related	Section 8.5.4
	Neurogenic bladder	Not related	Section 8.5.4
	Gastroenteritis, hip deformity, joint dislocation, epilepsy, pyelonephritis	Not related	Sections 8.5.4 and 8.5.5.6
	Bacterial diarrhea	Not related	Section 8.5.4
	Device malfunction	Not related	Section 8.5.4
	UTI	Related	Section 8.5.5.6 (pyelonephritis)
	Pyelonephritis	Not related	Section 8.5.5.6
	UTI	Related	Section 8.5.5.1
	UTI	Not related	Section 8.5.5.1
	UTI	Not related	Section 8.5.5.1
	Hydronephrosis	Not related	Section 8.5.5.4
	PDSOT	Not related	Section 8.5.5.7
	PDSOT	Not related	Section 8.5.5.7
	PDSOT	Not related	Section 8.5.5.7
	PDSOT	Not related	Section 8.5.5.7
	PDSOT	Not related	Section 8.5.5.7

Source: Module 5.3.5.3 Integrated Summary of Safety, PDSOT, DC and SAE Narratives
Abbreviations: PDSOT, potential distant spread of toxin; SAE, serious adverse event; UTI, urinary tract infection

Narrative Descriptions

Patient (b) (6): 13-year-old boy with spina bifida since (b) (6), hydrocephalus, meningomyelocele L5-S1 with closure, detrusorotomy, vesicoureteral reflux grade 3 on the left, and grade 4 on the right, absence of Achilles tendon reflex, bilateral trabeculation of the bladder, constipation and flexible pes planovalgus bilaterally. His concomitant medications included oral ciprofloxacin, cefazolin, nitrofurantoin, amoxicillin with clavulanate, lactated Ringer's solution, ibuprofen, fusidic acid for limb injury, solifenacin, oxybutynin, tolterodine and fesoterodine. On June (b) (6) he received BOTOX 200 U in study 191622-120. On (b) (6) 277 days later, he experienced epididymitis and orchitis. He had a painful red scrotum and ultrasound confirmed the diagnosis. He was hospitalized and he was treated with intravenous amoxicillin and

clavulanate for 3 days and the infection resolved by [redacted] (per amended report sent after information request on October 5, 2020). The investigator considered the event serious due to hospitalization, unrelated to study treatment.

Clinical Reviewer's Comment: *The event is serious but unrelated to study treatment.*

Patient [redacted]: 16-year-old boy with spinal cord injury at L1 since [redacted]. He had sickle cell anemia, blood iron overload, chronic hemolysis, functional asplenia, muscular spasm, convulsions, cerebral medullary ischemia, recurrent UTI and a cholecystectomy. Concomitant medications included folic acid, deferiprone, baclofen, valproate sodium, vitram B, vitamin D, Fosfomycin trometamol for UTI, phenoxymethylpenicillin for asplenia, and oxybutynin. He had an arteriovenous fistula for plasma exchange for his sickle cell disease. He received BOTOX 50 U on [redacted] in study 191622-120. On [redacted], 61 days after administration, he experienced an arteriovenous fistula thrombosis and was hospitalized for repair. The event was considered resolved on [redacted]. The event was considered serious and unrelated.

Clinical Reviewer's Comment: *The event is serious but unrelated to study treatment.*

Patient [redacted]: 11-year-old girl with spina bifida, multiple occurrences of pyelonephritis, paraplegia psychic tractor and precocious puberty. She was taking carbamazepine for epilepsy and oxybutynin. She received BOTOX 50 U on [redacted] in study 191622-120. On [redacted] she underwent orthopedic surgery for kyphosis. On [redacted] 90 days after BOTOX administration, she developed a postoperative wound infection with a culture positive for Enterobacter cloacae. She underwent two more surgeries to clean out the wound, and was treated with cefepime, amikacin, meropenem, sulfamethoxazole-trimethoprim, and ciprofloxacin, as well as morphine. The infection resolved on [redacted]. The event was considered serious due to hospitalization and not related to study treatment.

Clinical Reviewer's Comment: *The event is serious but unrelated to study treatment.*

Patient [redacted] 6-year-old girl with spina bifida, hydrocephalus, ventriculoperitoneal shunt, vesicoureteral reflux grade 3 to 4 with endoscopic sling procedure of the ureters. She was taking lactulose, furazidine, solifenacin and oxybutynin. She received 100 U BOTOX on [redacted] On [redacted] 87 days after BOTOX administration, she experienced hydrocephalus with headache, vomiting, somnolence and convulsions. She was admitted, imaged, and was treated with paracetamol, mannitol, metamizole magnesium, phenobarbital, acetaminophen, amoxicillin clavulanate, ibuprofen, diazepam and electrolytes. The hydrocephalus resolved on [redacted] However, that same day she was diagnosed with viral encephalitis and developed status epilepticus. She was intubated, received intravenous acyclovir, cefotaxime, ranitidine, cefuroxime, paracetamol, dexamethasone, oral nystatin, ambroxol hydrochloride, omeprazole, prednisone, dextrose and sodium chloride. The event

resolved on (b) (6) and she was discharged home. The events were considered serious, life-threatening, requiring hospitalization, but not related to study treatment.

Clinical Reviewer's Comment: *The events are serious and not related to study treatment.*

Patient (b) (6): 9-year-old boy with caudal regression syndrome, neurogenic bladder and bowel, bulbar stricture of urethra and disturbed attention control. Concomitant medications included methylphenidate hydrochloride, antibiotics for UTI and fesoterodine fumarate. He received BOTOX 200 U on (b) (6) in study 191622-120. He entered the extension study and received BOTOX 200 U on (b) (6) On (b) (6) 119 days after administration, he developed nasopharyngitis, followed by the development of pneumonia of moderate severity on (b) (6) He was admitted and treated with intravenous ceftriaxone and oral amoxicillin clavulanate. The pneumonia resolved on (b) (6) The event was assessed as serious and not related.

Clinical Reviewer's Comment: *The event is serious and not related to study treatment.*

Patient (b) (6) 12-year-old boy with spina bifida and hydrocephalus, status post sacral myelomeningocele repair and ventriculoperitoneal shunt placement, constipation, bilateral hydronephrosis, bilateral inguinal hernias (repaired), and knee pain. He was on trimethoprim, macrogol and oxybutynin. He received BOTOX 100 U on (b) (6) in study 191622-120 and entered the extension study where he received BOTOX 200 U on (b) (6) On (b) (6) he presented for a consultation regarding bilateral great toe deformity and the SAE of left foot deformity was reported. On (b) (6) 149 days after administration of BOTOX, the patient developed arthritis at the metatarsophalangeal joint of moderate severity. The patient underwent fusion of the first left metacarpophalangeal joint and distal interphalangeal joint and a medial column release and lateral wiring on (b) (6). The event resolved and the patient was discharged on (b) (6) The patient received morphine and acetaminophen for pain through (b) (6) at which point the postoperative pain resolved. The event of foot deformity was assessed as serious and not related to study treatment.

Clinical Reviewer's Comment: *This reviewer agrees, the event is serious and unrelated to study treatment.*

Patient (b) (6): 8-year-old boy with spina bifida, latex allergy, short left calcaneal tendon, Achilles tendon extension, tethered cord recovery, hemi-epiphysiodesis, and tooth abscess. Concomitant medications included acetaminophen and flucloxacin and Fosfomycin for infections. He received BOTOX 100 U ion (b) (6) in study 191622-121, and entered the extension study and received BOTOX 200 U on (b) (6) and (b) (6) On (b) (6) 36 days after administration of the first BOTOX 200 U dose in study 191622-121, he developed a left foot wound infection, which had developed from a blister that opened. He was treated with topical fucidic acid and alginogel, but developed fevers to 38.8°C on (b) (6)

with stranding developing in the leg to the upper thigh. He was admitted for intravenous flucloxacillin x 14 days. His initial WBC was 13,000, wound and blood cultures were positive for Staphylococcus aureus. His urine also had WBC, bacteria and staphylococcus. He had vacuum assisted closure of the wound for 10 days. He was discharged on (b) (6) to use topical hydrogel and silver sulfate foam bandages. The wound infection was resolved on (b) (6) however, it recurred on (b) (6) 219 days after BOTOX administration. This was treated with topical silver sulfate foam bandage and intrasite topical. The event was ongoing. The Applicant assessed the event as serious and not related.

Clinical Reviewer's Comment: *The event is serious and not related to study treatment.*

Patient (b) (6): 16-year-old boy with spinal cord injury at L1 since (b) (6). He had sickle cell anemia, blood iron overload, chronic hemolysis, functional asplenia, muscular spasm, convulsions, cerebral medullary ischemia, recurrent UTI and a cholecystectomy. Concomitant medications included folic acid, deferiprone, baclofen, valproate sodium, vitram B, vitamin D, Fosfomycin trometamol for UTI, phenoxymethylpenicillin for asplenia, oxybutynin. He had an arteriovenous fistula for plasma exchange for his sickle cell disease. He received BOTOX 50 U on (b) (6) in study 191622-120 and BOTOX 100 U on (b) (6) and (b) (6) in study 191622-121. He had repair of the arteriovenous fistula after a thrombus on (b) (6) (described above). The repair failed and on (b) (6), 3 days after the first dose of 100 U BOTOX in the extension study, he was admitted for fistula closure and repair. He had postoperative pain on (b) (6) with sensory loss. The repair was resolved, but the pain and sensory loss were ongoing. The Applicant assessed the event as serious and not related.

Clinical Reviewer's Comment: *The event is serious but unrelated to study treatment.*

Patient (b) (6): 13-year-old girl with spina bifida, heel cord contracture, planovalgus feet status postsurgery, hydrocephalus with right ventriculoperitoneal shunt, closure of myelomeningocele, neurogenic bowel, bilateral hip dysplasia with surgeries, neuromuscular scoliosis, tachycardia, tethered spinal cord release with carbon dioxide and wound explorations, Arnold-Chiari malformation type 2. Concomitant medications included oxybutynin, glycerol for cecostomy irrigation, nitrofurantoin, azithromycin, paracetamol, ondansetron, oxycodone. She received BOTOX 50 U on (b) (6) in study 191622-120 and BOTOX 100 U on (b) (6) in study 191622-121. 145 days after the second dose of BOTOX, she decided to have an appendicovesicostomy for bladder augmentation and exited the study. The event was classified as neurogenic bladder. This event was not considered related to study treatment.

Clinical Reviewer's Comment: *This reviewer agrees, the event is serious due to hospitalization for surgery, but is related to the underlying condition and not to study treatment.*

Patient (b) (6): 10-year-old male with spina bifida, neurogenic bladder, a history of pyelonephritis, on cefuroxime for prophylaxis of UTI. He received 100 U BOTOX in study

191622-120 on (b) (6). He then got 100 U BOTOX on (b) (6) in study 191622-121. On (b) (6) 52 days after administration of BOTOX 100 U in the extension study, he developed hip deformity and left hip joint dislocation. He was hospitalized and underwent bilateral varus derotation osteotomy, bilateral hamstring release, and left adductor and psoas release. The event resolved and he was discharged to home on (b) (6). On (b) (6) he developed gastroenteritis and influenza and on (b) (6) developed pyuria and was hospitalized for antibiotic treatment with temocillin. The pyuria resolved on (b) (6) and the next day the influenza resolved, but he developed gastroesophageal reflux disease (GERD) and was treated with ranitidine with resolution by (b) (6). The GERD was ongoing. On (b) (6) 210 days after the administration of the second 100 U BOTOX dose in the extension study, he had increased seizure activity and was hospitalized for the event of epilepsy. He had no seizures in the hospital, no changes were made to his medications and he was discharged on (b) (6) These events were all considered serious and unrelated to treatment. (Separate event of pyelonephritis described below in Section 8.5.5.6.)

Clinical Reviewer's Comment: *the events of hip deformity, gastroenteritis, influenza, GERD and epilepsy are unrelated to study treatment.*

Patient (b) (6): 5-year-old boy with spina bifida who was taking only oxybutynin. She received BOTOX 100 U on (b) (6) in study 191622-120 and BOTOX 100 U on (b) (6) in study 191622-121. On (b) (6) he developed bacterial diarrhea due to Salmonella and fever. He was hospitalized on (b) (6) and he received *saccharomyces boulardii*, acecadotrik, cefotaxime, amoxicillin and paracetamol. The fever resolved on (b) (6) and the diarrhea resolved on (b) (6) The events were assessed as unrelated to study treatment.

Clinical Reviewer's Comment: *The event of bacterial diarrhea is serious and unrelated to study treatment.*

Patient (b) (6): 16-year-old girl with spina bifida, hydrocephalus with a ventriculoperitoneal shunt, and headaches, on paracetamol and solifenacin. She received BOTOX 200 U on (b) (6) in study 191622-120 and BOTOX 200 U on (b) (6) and (b) (6) in study 191622-121. On (b) (6) 58 days after the first dose of BOTOX in the extension study, she had a headache, underwent computed tomography scanning and was found to have a malfunction of the ventriculoperitoneal shunt. She was hospitalized and received dexamethasone, cefazolin, akritoin, paracetamol, ketoprofen, ondansetron, midazolam, amikacin and ceftriaxone. She also developed psoriasis in the hospital. On (b) (6) she underwent shunt revision and was diagnosed with bronchitis that day. She had budesonide, ambroxol and salbutamol added to her medications. The events of device malfunction, bronchitis and psoriasis resolved. Subsequently, on (b) (6), 249 days after BOTOX, she developed pharyngitis treated with amoxicillin but got a fever 3 days later. She had ciprofloxacin, devuroxime, hydrocortisone, ibuprofen, omeprazole, cefotaxime, dexamethasone, paracetamol and salbutamol added to her regimen. Blood and urine cultures

were negative. The fever resolved on (b) (6) These events were all considered not related to study treatment.

Clinical Reviewer's Comment: *The events are not related to study treatment.*

Overall Reviewer Comment: *The clinical reviewer concurs that the SAEs described above are not related to the BOTOX drug or its administration. Please see below in Vital Signs, and Sections 8.5.5.1, 8.5.5.4, 8.5.5.6 and 8.5.5.7 for reviews of additional SAE narratives pertaining to hypertension, UTI, pyelonephritis, hydronephrosis and PDSOT.* ***Overall, the SAEs do not display a trend by dose****.*

Dropouts and/or Discontinuations Due to Adverse Effects

One patient (Patient (b) (6)) discontinued from study 191622-120 due to a STEAE of cystitis in the 50 U BOTOX group. The event was reported 126 days after study drug administration. The patient was hospitalized and treated with antibiotics with resolution 16 days after onset. The event was considered related to the study drug.

One patient (Patient (b) (6)) discontinued due to a TEAE in study 191622-121. The patient decided to have an appendicovesicostomy to augment the bladder after receiving BOTOX 100 U and was discontinued from the study. The event was considered not related to the study drug.

Significant Adverse Events

See Section 8.5.5 for significant adverse events which are submission-specific issues.

Treatment-Emergent Adverse Events and Adverse Reactions

In study 191622-120, 73.5% (83/113) of patients reported at least one TEAE (71.1% [27/38], 73.3% [33/45]), and 76.7% [23/30] in the 50 U, 100 U, and 200 U BOTOX groups, respectively).

Treatment-related TEAEs (related to the study drug or injection procedure or both), were reported by 14.2% (16/113) of patients overall (2.6% [1/38], 22.2% [10/45]), and 16.7% [5/30] in the 50 U, 100 U, and 200 U BOTOX groups, respectively). Most were assessed as related to the study injection procedure. The most commonly reported TEAEs during the first 12 weeks of treatment were UTI and bacteriuria (19.5% [22/113] and 14.2% [16/113], respectively). The Applicant did not identify any dose relationship for TEAEs through the duration of the study among the three treatment groups. Ten patients received a dose less than that assigned due to the 6 U/kg body weight cap (nine patients assigned to 200 U and 1 assigned to 100 U) and there was no difference in safety findings among that subset of patients.

In study 191622-121, 76.8% of patients reported at least one TEAE during Treatment Cycle 1, 80.0% during Treatment cycle 2, 63.6% in Treatment Cycle 3 and 81.8% in Treatment Cycle 4. Most of the treatment related TEAEs again were considered related to study drug injection.

Adverse drug reactions were identified as UTI, bacteriuria, and leukocyturia, hematuria and blood urine present. These are reviewed in Sections 8.5.5.1, 8.5.5.2 and 8.5.5.3.

Clinical Reviewer's Comment*: This clinical reviewer analyzed TEAEs by dose and found no dose relationship between 50 U, 100 U and 200 U doses.*

Laboratory Findings

The Applicant reported that for Treatment Cycle 1 there were no TEAEs based on postbaseline potentially clinically significant laboratory results for chemistry, hematology or quantitative urinalysis parameters. There was one patient in the BOTOX 50 U dose group with a raised serum creatinine level at the Week 12 visit, but this was not reported as a TEAE. With repeated cycles, there were reports of potentially clinically significant values in serum creatinine, bicarbonate, bilirubin, blood urea nitrogen, calcium, magnesium, phosphate, glucose, protein, uric acid, alkaline phosphatase. Only one of these was reported as a TEAE in one subject in the 50 U BOTOX dose group during Treatment Cycle 2. There were also reports of potentially clinically significant values in hematocrit, hemoglobin, leukocytes, lymphocytes, monocytes, neutrophils, eosinophils and platelets, but only one was reported as a TEAE in a patient in the 100 U BOTOX group (low hemoglobin/hematocrit) in Treatment Cycle 2. There were no potentially clinically significant values in urinalysis parameters. There were no dose-related trends for any of the laboratory findings.

Clinical Reviewer's Comment: *The clinical reviewer examined the database for shift changes out of the normal range and confirmed the Applicant's assertions. Any abnormalities, for example in white blood cell count, were accounted for SAE narratives, for example in the narratives for Patient* (b) (6) *with a UTI and Patient* (b) (6) *with pyelonephritis.*

Vital Signs

Blood Pressure

The Applicant reports one subject with an SAE of hypertension in Treatment Cycle 1.

Patient (b) (6) was an 8-year-old male with spina bifida, headache, hydrocephalus and shunt implantation, kidney asymmetry (smaller right kidney) and a pre-existing history of hypertension. He received 200 U BOTOX on (b) (6) in study 191622-120. Concomitant medications included oral cefuroxime axetil for pharyngitis, oral enalapril maleate and oral amlodipine besilate for hypertension, oral cefuroxime sodium for respiratory tract infection, intravenous cefazoline sodium as antibiotic prophylaxis and oral oxybutynin hydrochloride for NDO. At baseline, the day prior to the administration of BOTOX 200 U, the participant's blood pressure was 115/70 mm Hg. On (b) (6), his blood pressure was 156/122. On (b) (6), his blood pressure was 140/100. In (b) (6) his antihypertensive enalapril maleate was increased from 5 mg daily to 7.5 mg daily with little effect. On (b) (6), he was admitted to the pediatric cardiology clinic for

management of his hypertension. His lab and radiographic tests were reported as normal and he was diagnosed with chronic renal failure and secondary hypertension. His medication was changed to amlodipine besilate. On [redacted], his blood pressure was 126/97 and on [redacted] at study completion, his blood pressure was 147/124. The event was ongoing and considered serious but unrelated to the study treatment.

The Applicant also notes two patients in the 50 U BOTOX group who had TEAEs of moderate hypertension during the study, but did not have clinically significant elevated blood pressure values recorded (Patient [redacted] who had pre-existing hypertension and Patient [redacted] who did not). Neither event was reported as serious or related to study treatment.

Clinical Reviewer's Comment: *The clinical reviewer agrees that the hypertension experienced by Patient [redacted] was serious and not related to study treatment. This reviewer also examined the database for instances of elevated systolic blood pressure (>140 mm Hg) and diastolic blood pressure (>90 mm Hg). Any instance of elevated blood pressure did not reveal a pattern by dose. There were eight patients who had multiple systolic blood pressure (SBP) recordings at visits which were in the range of 140s-170s; most were not accompanied by elevations in diastolic blood pressure (DBP). Patient [redacted] was the only subject who had repeated elevations of both systolic and diastolic blood pressure which was consistent with a pre-existing history of hypertension secondary to chronic renal failure. There was no trend by dose. No subject was diagnosed with autonomic dysreflexia, a known adverse reaction with BOTOX for the treatment of NDO.*

The database was similarly examined for instances of hypotension, with iterations going down to SBP <80 and DBP <40 (given that blood pressure in very young children can normally be this low). There were no differences in reductions in SBP or DBP by dose. The clinical reviewer does not have a concern for an association of hypertension or hypotension with BOTOX.

Pulse and Respiratory Rate

The Applicant reported that mean vital signs values changed little during the studies, and no differences between BOTOX dose groups were apparent.

Clinical Reviewer's Comment*: The reviewer queried the database for changes in pulse signaling tachycardia (iterations of pulse >100, >110, >120) and bradycardia (pulse <60), tachypnea and bradypnea and there were no significant mean changes in pulse or respiratory rate, nor any trends by dose.*

Electrocardiograms

Not applicable.

QT

Not applicable. BOTOX does not have an established arrhythmogenic potential.

Immunogenicity

It is known that patients may form NABs to botulinum toxin type A, which could reduce the effectiveness of BOTOX, or potentially affect the safety of the drug. The Applicant identified NABs through a two-step process. First serum results to BABs were analyzed and reported as negative, positive or inconclusive for all patients with analyzable serum samples. These samples were then tested for NABs using a mouse protection assay. If a sample contained NABs it was deemed protected, if it had no NABs it was reported as not protected, and if it was inconclusive, it was reported as inconclusive.

Eighteen patients tested positive for BABs, and none were positive for NABs at any BOTOX dose. Among the 18 patients, 15 tested positive for BABs after receiving BOTOX. Two of the 18 patients were positive for BABs at baseline (predose) and negative for BABs after treatment and therefore considered false positive for BABs. One of the 18 patients tested positive for BABs at baseline and had no immunogenicity testing results after treatment and is considered inconclusive. The Applicant asserted that there were no changes in the safety profile of those patients who developed BABs.

The Applicant provided the following table of pooled data from Studies 191622-120 and 191622-121 to support this assertion:

Table 30. Adverse Events by Binding Antibody Status

TEAE Type	BAB Positive (N=15) n(%)	BAB Negative (N=93) n(%)	Total (N=108) n(%)
All TEAEs	15 (100.0)	83 (89.2)	98 (90.7)
Treatment-related TEAEs	4 (26.7)	28 (30.1)	32 (29.6)
Study injection procedure-related TEAEs	4 (26.7)	24 (25.8)	28 (25.9)
Study drug-related TEAEs	0	7 (7.5)	7 (6.5)
All serious TEAEs (STEAES)	3 (20.0)	16 (17.2)	19 (17.6)
Treatment-related STEAEs	1 (6.7)	2 (2.2)	3 (2.8)
Discontinue study due to TEAEs	0	2 (2.2)	2 (1.9)
Death	0	0	0

Source: Applicant's submission
Only treated participants with analyzable immunogenicity samples postbaseline (after first treatment) are included in this table.
BAB Positive = Participants with at least one positive postbaseline result for Toxin-Binding Ant body. BAB Negative = Participants with only negative postbaseline result(s) for Toxin-Binding Antibody
Abbreviations: BAB, binding ant body; TEAE, treatment-emergent adverse event

Clinical Reviewer's Comment: *There are a small number of patients who had sample analyzable for development of BABs or NABs. However, among this small population, there does not appear to be any effect on safety of BOTOX due to the development of BABs. See also Section 6.3.1 for the Clinical Pharmacology review of Immunogenicity.*

8.5.5. Analysis of Submission-Specific Safety Issues

Safety issues that are specific to intradetrusor injection of BOTOX include UTI, hematuria, hydronephrosis, vesicoureteric reflux, pyelonephritis potential distant spread of toxin (PDSOT) and immunogenicity. Each of these safety concerns and their frequency in Studies 191622-120

and 191622-121 is described below, except for immunogenicity which has already been described above.

There were no cases of autonomic dysreflexia, renal failure or nephrolithiasis and no hypersensitivity reactions, therefore these are not described.

8.5.5.1. Urinary Tract Infection

An adverse event of UTI was defined as a symptomatic UTI that required treatment in the opinion of the investigator. The factors for making this diagnosis included symptoms and signs of UTI (such as fever, flank pain, dysuria and changes in urinary pattern) as well as bacteriuria and leukocyturia. The lab criteria were not strict, as these patients commonly have bacteriuria, which could be colonization or infection, due to the underlying condition and need for CIC. Urinalysis or culture results which were clinically significant but did not meet this definition were still classified as adverse events, but as bacteriuria or leukocyturia. UTI was assessed for within 2 weeks of injection, within 12 weeks of injection, and over the full treatment cycle.

UTIs were the most frequently reported TEAEs.

- UTI within 2 weeks of injection was rare, occurring in 3.5% of patients in study 191622-120 and among patients in study 191622-121, at 4.2%, 5.6%, 7.3% and 0% in Cycles 1, 2, 3 and 4 respectively.
- UTI within 12 weeks occurred in 22/113 patients (19.5%) overall in study 191622-120. In study 191622-121 the rates were overall slightly higher at21.1%, 20.0% and 18.2% during Treatment Cycles 2, 3, and 4 respectively, compared to 16.8% during Treatment Cycle 1 in study 191622-20.
- The overall frequency of UTI over the full treatment cycle was 30.5%, 34.4%, 21.8%, and 18.2%, during Treatment Cycles 1, 2, 3, and 4, respectively.

There was no discernable pattern in the incidence of UTI between dosage groups or with repeated injection.

Table 31. Incidence of Treatment-Emergent UTI During Entire Cycle

Study Treatment Cycle	BOTOX 50 U n/N (%)	BOTOX 100 U n/N (%)	BOTOX 200 U n/N (%)	Total n/N (%)
Study 191622-120				
Cycle 1	11/38 (28.9)	15/45 (33.3)	7/30 (23.3)	33/113 (29.2)
Study 191622-121				
Cycle 1[1]	9/31 (29.0)	14/39 (35.9)	5/25 (20.0)	28/95 (29.5)
Cycle 2	1/9 (11.1)	21/45 (26.7)	9/36 (25.0)	31/90 (34.4)
Cycle 3	0/5 (0)	4/16 (25.0)	8/34 (23.5)	12/55 (21.8)
Cycle 4	1/3 (33.3)	1/4 (25.0)	0/4 (0)	2/11 (18.2)

Adapted from Table 2-13 Summary of Clinical Safety (p.40/55)
[1] Patients from 191622-120 in extension study
Abbreviations: UTI, urinary tract infection

Annualized rates of UTI in study 191622-120 were similar among all dosage groups and did not indicate an increase in the risk of UTI compared to pretreatment.

Table 32. Study 190622-120 UTI Event Rate Per Patient Year

Time of Event	BOTOX 50 U N=38	BOTOX 100 U N=45	BOTOX 200 U N=30
6 months prior to screening	0.47	0.98	0.93
Treatment period	0.67	1.01	0.57

Adapted from CSR 191-622-120 Table 14.3-7.2
Abbreviations: UTI, urinary tract infection

Narratives for UTIs That Were Considered Serious Adverse Events:

Study 191622-120:

- Participant (b) (6): 12-year-old female with a history of dysuria, hydronephrosis, neurogenic bowel, a history of UTIs, asymptomatic bacteria and CIC. She previously had *Escherichia coli* UTI twice. She Received BOTOX 50 U on (b) (6). On (b) (6) (27 days later), she had a positive urine culture and unspecified symptoms. She was hospitalized with a fever, but was noted as "afebrile." She received intravenous piperacillin/tazobactam and paracetamol for abdominal pain. The event resolved and she was discharged (b) (6) with Bactrim to be administered orally. This event was considered by investigator and Allergan as serious (hospitalization) and not related to BOTOX.

Clinical Reviewer's Comment*: During the study, UTI events were assessed at 2 weeks and 12 weeks after injection. Given that the event of UTI occurred technically within 30 days of BOTOX administration, it is possibly related. This event is serious as it resulted in hospitalization.*

- Patient (b) (6) 8-year-old male with a history of neurogenic bowel, hydrocephalus, a ventriculo-external drain and a peritoneal drain. He was on nitrofurantoin for UTI prophylaxis, had previously received intravenous (IV) tobramycin for a UTI (unclear dates) and was on oxybutynin and fesoterodine fumarate for NDO, overactive bladder, incontinence and noncompliant bladder. He received BOTOX 50 U on (b) (6). 29 days later on (b) (6) he presented with a UTI with fever and was hospitalized and received IV cefotaxime. The symptoms resolved on (b) (6) He was discharged home on amoxicillin/clavulanic acid and the UTI was considered resolved on (b) (6) Again on (b) (6) 95 days after BOTOX administration, he developed a UTI, fever and dehydration. He was hospitalized for a lower UTI (which was initially thought to be pyelonephritis). He was treated with cefotaxime and paracetamol and the event resolved on (b) (6) with discharge home that day. He was readmitted with fever (b) (6) and was given antibiotics for a UTI but the urine culture was negative. He was discharged on (b) (6). Again on (b) (6), 126 days later, he developed cystitis, was admitted and received cefotaxime and oxybutynin. The cystitis resolved on (b) (6), and he was discharged on (b) (6) He discontinued from the study due to cystitis. The Applicant assessed this as serious and unrelated.

Clinical Reviewer's Comment*: This patient has a chronic history of UTIs and had several instances during the study, so these events most likely are due to his underlying condition. So it could be considered unrelated to study drug administration.*

- Patient (b) (6): 16-year-old male who received 100 U BOTOX on (b) (6). He had meningomyelocele and a history of UTIs, and was on nitrofurantoin, ciprofloxacin and cefprozil for prophylaxis. He was also taking propiverine hydrochloride and fesoterodine fumarate for urinary incontinence. Seventy-eight days after BOTOX administration he presented to the hospital with a stomach ache and fever and was admitted for the suspicion of acute appendicitis. However, he had elevated urine leukocytes of 425, elevated C-reactive protein of 37.32 and elevated white blood cell count of 15.96 (no values or ranges provided). He was treated with ibuprofen, paracetamol and cefazolin. A urine culture after start of antibiotics was negative. The event resolved on (b) (6).

Clinical Reviewer's Comment*: This event is serious and not related to the treatment but more likely related to the underlying process; the subject has a history of UTIs and was on multiple antibiotics for prophylaxis.*

- Patient (b) (6): 5-year-old male with spina bifida whose only concomitant medication was oxybutynin. He received BOTOX 100 U on (b) (6). On (b) (6), 82 days after injection, he was diagnosed with a UTI with symptoms of dysuria and acute urinary retention. He was admitted on (b) (6). A urine culture grew Enterococcus faecalis. He was treated and discharged home on (b) (6) on oral amoxicillin. The Applicant assessed as the event as serious and not related.

Clinical Reviewer's Comment*: The event is serious and not related.*

- Study 191622-121: Patient (b) (6) was an 8-year-old male with a history of spina bifida, small right kidney, on amoxicillin/clavunate for UTI prophylaxis. He received 200 U BOTOX on (b) (6) in study 191622-120 and 200 U BOTOX on (b) (6) and (b) (6) in study 191622-121. On (b) (6), 14 days after injection, he had a UTI and macroscopic hematuria with "redness" in the bladder area. He was admitted to the hospital and received intravenous ciprofloxacin and paracetamol. On (b) (6) urine culture was negative. The hematuria resolved on (b) (6), fever resolved on (b) (6) and he was discharged to home on (b) (6) with amoxicillin which was later changed to amoxicillin/clavunate. The event resolved on (b) (6) The event was assessed as serious and not related to the study drug, but related to the administration procedure.

Clinical Reviewer's Comment*: The reviewer concurs with the investigator assessment.*

- Patient (b) (6): 8-year-old female with spina bifida and neurogenic sphincter disorder, getting CIC six times per day. She was taking Bactrim for cough. She got 50 U on (b) (6)

(b) (6) in study 191622-120. In study 191622-121, she received 100 U on (b) (6) (b) (6) and 200 U on (b) (6) On (b) (6) 168 days after the 100 U BOTOX injection, she had a UTI, was treated with Bactrim, with resolution of the event on (b) (6) At the beginning of (b) (6) she was found to have turbid urine for 1 week. She was treated with oral amoxicillin/clavulanate without improvement (but had vomiting on it). On (b) (6) 42 days after getting 200 U BOTOX, she was admitted with a UTI. She had suprapubic tenderness but no fever and a urine culture grew *Enterococcus faecalis*. She was treated with intravenous ampicillin and the event resolved (b) (6) The case was assessed as not related.

Clinical Reviewer's Comment*: These two events of UTI are not related to study treatment. While the first UTI appears nonserious, the second event was serious as it resulted in hospitalization.*

- Patient (b) (6): 12-year-old female with a history of spinal cord injury at T3, on nitrofurantoin for UTI prophylaxis, as well as amoxicillin/clavulanate upper respiratory infection. She was also taking fesoterodine. She does CIC. She received 100 U BOTOX on (b) (6) in study 191622-120. She subsequently got BOTOX 200 U on (b) (6) 2016 and (b) (6) in study 191622-121. On (b) (6) 174 days after the first BOTOX injection in study 191622-121, she developed a UTI with symptoms of inguinal pain, fever and an inability to void. She was admitted, got IV hyoscine butyl bromide (scopolamine), cefazolin, cefoperazone, sulperazon and paracetamol. Her C-reactive protein was 123.1, absolute neutrophil count was 63.7%, an white blood cell count was 14.58 on (b) (6) By (b) (6), her fever subsided, her lab values were trending toward the normal range and the incident was considered resolved. She was discharged home on oral antibiotics. The investigator assessed the event as serious and unrelated.

Clinical Reviewer's Comment*: Reviewer agrees; the event is serious and unrelated to study treatment.*

Overall Clinical Reviewer's Comment*: The overall incidence of UTI does not differ between dose groups or with repeated injection. As the Applicant notes, annualized rates of UTI were similar among all dose groups and did not indicate an increase in the risk of UTI compared to pretreatment. Again, it is important to note that number of patients are very small in cycle 4, and for the 50 U dose group, very small after the first cycle; therefore, those groups have limited data for interpretation. The serious adverse events of UTI noted in the narratives included only three cases which could be considered related to the study injection procedure: one occurred within 14 days of study drug injection and two occurred within 30 days. The remainder of the cases are unrelated to treatment administration and more likely related to the underlying condition.*

There were three cases which the Applicant classified as UTIs but that were more consistent with pyelonephritis based on symptoms and findings. Patient (b) (6) was classified by the

investigators as a UTI, but he had two events one of which this reviewer finds was more consistent with pyelonephritis, so I have placed the narrative in the pyelonephritis section. Patient (b) (6) *was classified by the investigator as a UTI for one event and pyelonephritis for another event, but the incidents are similar so I have placed the narrative in the pyelonephritis section. Patient* (b) (6) *was classified as a UTI but the patient was febrile to 106 degrees Fahrenheit; therefore, this serious adverse event should be classified as pyelonephritis. See Section 8.5.5.6 for these narratives.*

8.5.5.2. Bacteriuria

Bacteriuria was reported quite frequently in the studies.

Table 33. Overall TEAE of Bacteriuria

Study Number Treatment Cycle	BOTOX 50 U n/N (%)	BOTOX 100 U n/N (%)	BOTOX 200 U n/N (%)	Total n/N (%)
Study 191622-120				
Cycle 1	6/38 (15.8)	7/45 (15.6)	6/30 (20.0)	19/113 (16.8)
Study 191622-121				
Cycle 1[1]	5/31 (16.1)	7/39 (17.9)	5/25 (20.0)	17/95 (17.9)
Cycle 2	1/9 (11.1)	9/45 (20.0)	2/36 (5.6)	12/90 (13.3)
Cycle 3	0/5 (0)	3/16 (18.8)	4/34 (11.8)	7/55 (12.7)
Cycle 4	2/3 (66.7)	2/4 (50.0)	2/4 (50.0)	6/11 (54.5)

Adapted from Clinical Summary of Safety, Table 2-2 and study 191622-121 Clinical Study Report Table 12-5
[1] Patients from 191622-120 in extension study

Clinical Reviewer's Comment*: Bacteriuria is quite common in this patient population due to the underlying condition and the need for CIC. The total subject numbers are quite small with increasing number of cycles, especially for the 50 U dose; therefore, meaningful conclusions cannot be drawn from Cycle 4. There is no discernible difference in the incidence, or a detectable pattern, of bacteriuria related to increasing doses or to cycle of treatment.*

8.5.5.3. Hematuria

The Applicant included hematuria events classified as study drug-related and injection-related TEAEs. Study drug-related TEAEs were reported during Treatment Cycles 1 and 2 only. The Applicant separated the term "hematuria" from "blood urine present." This reviewer finds these two terms should be combined. In the Applicant's Table 2-10 in the Summary of Clinical Safety cataloguing TEAEs occurring in >3% of pediatric patients in study 191622-120, they included only injection-related hematuria; however, this reviewer finds events classified as study-drug-related should also be included. In the description of TEAEs in the Study Report for study 190622-121, they describe study drug-related hematuria separately from injection-related TEAES. For the purposes of analysis, this reviewer has combined them.

Table 34. Hematuria Adverse Events Through Treatment Cycle

Study Number Treatment Cycle Adverse Event	BOTOX 50 U n/N (%)	BOTOX 100 U n/N (%)	BOTOX 200 U n/N (%)	Total n/N (%)	FDA Reviewer Total
Study 191622-120					
Cycle 1					
Hematuria[1]	2/38 (5.2)	1/45 (2.2)	1/30 (3.3)	3/113 (2.7)	5/113 (4.4)
Blood urine present[3]	0/38 (0)	2/45 (4.4)	0/30 (0)	2/113 (1.7)	
Study 191622-121					
Cycle 1[2]					
Hematuria[1]	2/31 (6.4)	1/39 (2.5)	1/25 (4.0)	3/95 (3.2)	5/95 (5.2)
Blood urine present[3]	0/31 (0)	2/39 (8.0)	0/25 (0)	2/95 (2.1)	
Cycle 2					
Hematuria[1]	0/9 (0.0)	0/45 (0.0)	0/36 (0.0)	0/90 (0.0)	7/90 (7.8)
Blood urine present[3]	2/90 (2.2)	3/90 (3.3)	2/90 (2.2)	7/90 (7.8)	
Cycle 3					
Hematuria[1]	0/5 (0.0)	0/16 (0.0)	1/34 (2.9)	1/55 (1.8)	9/55 (16.3)
Blood urine present[3]	2/5 (40)	1/16 (6.2)	5/34 (14.7)	8/55 (14.5)	
Cycle 4					
Hematuria[1]	0/3 (0.0)	0/4 (0.0)	0/4 (0.0)	0/11 (0.0)	5/11 (45.5)
Blood urine present[3]	2/3 (66.7)	1/4 (25.5)	2/4 (50.0)	5/11 (45.5)	

Adapted from Table 2-10 Summary of Clinical Safety p.35/55 and Clinical Study Reports for Studies 190622-120 and 190622-121
[1] Includes study drug-related and injection related
[2] Patients from 191622-120 in extension study
[3] Includes only injection related

Clinical Reviewer's Comment*: Hematuria is an expected outcome with injection into the bladder wall, especially with multiple injections in a given procedure. Overall the rate of hematuria is low, at 4.4% in the first cycle and 7.8% in the second cycle. Most of the events are classified as study injection related as opposed to study drug-related. The rate of hematuria appears to increase in Cycles 3 and 4; however, the clinical reviewer believes that the proportions are overinflated due to decreasing sample size with increasing number of treatment cycles. There does not appear to be any correlation of increased incidence of hematuria with increasing doses of BOTOX.*

Clinical Reviewer's Comment: *For pediatric patients who were dosed at BOTOX 6 U/Kg body weight, the adverse reactions were similar to BOTOX 200 U dose. The adverse reactions included urinary tract infections, bacteriuria and hematuria.*

8.5.5.4. Hydronephrosis

Seven patients were reported to have hydronephrosis during both studies. This reviewer repeated the analyses for these events and reached the same results. The cases are as follows:

Three patients had hydronephrosis during study 191622-120. Two in the 50 U group:

- Patient (b) (6): who had a baseline history of intermittent hydronephrosis developed mild right sided hydronephrosis 85 days after BOTOX administration, ongoing at the end of the study.
- Patient (b) (6): mild bilateral hydronephrosis 132 days after drug administration, ongoing at the end of the study.

These events were not considered related to study drug.

- One patient in the 100 U group (Patient (b) (6), who had baseline hydronephrosis had mild right hydronephrosis 340 days after BOTOX administration. This was described as a worsening of pre-existing disease and not considered related to treatment.

There were no instances of hydronephrosis in the 200 U group in study 19162-120.

In the extension study, study 191622-121, two patients in the 100 U group in treatment Cycle 2 had hydronephrosis, and two patients in the 100 U group in treatment cycle 3 had hydronephrosis.

- Patient (b) (6): baseline history also included bladder stones, developed severe right sided hydronephrosis 87 days after BOTOX injection in Cycle 2. The event resolved 4 days later and was assessed as unrelated to study drug.
- Patient (b) (6): had a baseline history of hydronephrosis, with right sided findings at screening. This subject developed mild right sided hydronephrosis 409 days after study drug administration in Cycle 2 and the case was ongoing at the end of the study.
- Patient (b) (6) had a baseline history of intermittent vesicoureteral reflux and experienced moderated hydronephrosis 85 days after BOTOX injection in Cycle 3. The event was ongoing.
- Patient (b) (6): was found to have mild hydronephrosis at 102 days after BOTOX injection in Cycle 3.

There were no instances of hydronephrosis in the 50 U or 200 U groups in the extension study.

Clinical Reviewer's Comment*: The incidence of hydronephrosis in the study is low and more likely related to underlying disease than to the drug or drug injection procedure. There is no discernible relationship to dose or cycle of BOTOX.*

8.5.5.5. Vesicoureteric Reflux

There were two cases of vesicoureteral reflux reported, one in each of the two studies. This reviewer repeated the analysis which yielded the same findings.

- Patient (b) (6): received 200 U in study 191622-120, had a baseline history of vesicoureteral reflux, grade 3 on the left and grade 4 on the right, and reported "moderate bilateral flank pain due to vesicoureteral reflux" 1 month after study injection. This was not confirmed by voiding cystourethrogram at the time, but was confirmed at study exit with urodynamics with contrast. The event was ongoing.
- Patient (b) (6): received 100 U in Cycle 2 (study 191622-121) and experienced severe bilateral vesicoureteral reflux (grade 4+) 262 days after BOTOX administration. The event was confirmed at study exit with a voiding cystourethrogram and was ongoing at the end of the study.

The events were assessed as unrelated to the study drug.

Clinical Reviewer's Comment*: This reviewer agrees that the events were unrelated to the study drug. Patient* (b) (6) *had pre-existing vesicoureteral reflux. The event in Patient* (b) (6) *was remote from the time of injection and likely due to the underlying disease process.*

8.5.5.6. Pyelonephritis

The Applicant catalogued two cases of pyelonephritis reported as TEAEs during Treatment Cycle 2 (study 191622-121), both in the 100 U BOTOX group.

- Patient (b) (6): 8-year-old male with a history of spina bifida, febrile seizure, UTI and constipation. Concomitant medications included macrogol, amoxicillin for strep throat and sinusitis, paracetamol and ibuprofen, vaccinium macrocarpon and cefdinir for UTI and Bactrim for fever. He was also on tolterodine. He received 100 U BOTOX on (b) (6) in study 191622-120 then entered the extension study. In study 191622-121, he got 100 U BOTOX on (b) (6). 185 days later, had a fever to 104°F, headache, and urine culture with *Enterobacter asburiae*. He was admitted and was treated with IV ceftriaxone, meropenem, intravenous fluids, paracetamol and cefdinir. The event resolved (b) (6) and he was discharged home on Bactrim. On (b) (6) 239 days after BOTOX, the patient was diagnosed with pyelonephritis. He had fever and back pain. A culture was done but the results are not available. He was treated with Bactrim with no relief. On (b) (6) he was seen in the Emergency Department with a fever of 103.8, flank pain, cloudy urine, headache, decreased oral intake and nausea and vomiting. An ultrasound showed left renal pelvis wall thickening and debris, suggesting pyelonephritis. He was admitted (b) (6) got cefepime, paracetamol and intravenous fluids. A subsequent urine culture was negative. His fever resolved (b) (6) and he was discharged home that day with oral cefdinir. The investigator assessed this event as not related and serious.

Clinical Reviewer's Comment*: This reviewer agrees that the event is serious and not related due to the time course.*

- Patient (b) (6): 10-year-old male with spina bifida, neurogenic bladder, a history of pyelonephritis, on cefuroxime for prophylaxis of UTI. He received 100 U BOTOX in study 191622-120 on (b) (6) He then got 100 U BOTOX on (b) (6) in study 191622-121. On (b) (6) 231 days later, he was diagnosed with pyelonephritis. He was admitted (b) (6) and was treated with intravenous ceftazidime and ciprofloxacin. The event resolved on (b) (6) and he was discharged home. The investigator assessed the event as serious and unrelated.

Clinical Reviewer's Comment*: This reviewer agrees, that the event is serious and unrelated due to the time course.*

This reviewer identified two other possible pyelonephritis cases, one from study 190622-120, which was classified by the Applicant as a urinary tract infection and other case from study 191622-121.

- Patient (b) (6) (study 191622-120) was a 16-year-old male who received 100 U BOTOX on (b) (6) He had meningomyelocele and a history of UTIs, and was on nitrofurantoin, ciprofloxacin and cefprozil for prophylaxis. He was also taking propiverine hydrochloride and fesoterodine fumarate for urinary incontinence. 331 days after BOTOX administration, on (b) (6) the patient was hospitalized for possible pyelonephritis, and received paracetamol, ibuprofen, cefuroxime and refroze. No further details about laboratory testing were provided. The infection resolved on (b) (6)

Clinical Reviewer's Comment*: This subject had a UTI (discussed above in Section 8.5.5.1) and a separate incident which I reclassified as pyelonephritis. The incident is serious and unrelated to study treatment.*

- Patient (b) (6): 13-year-old male with a history of spina bifida, grade 3 left vesicoureteral reflux, constipation, neurogenic bowel, asymptomatic bacteriuria (with *Streptococcus agalactiae* and *E. faecalis*), and *E. coli* colonization. Medications included docusate and oxybutynin. He received 200 U BOTOX on (b) (6) in study 191622-120. In study 190622-121, he got 200 U of BOTOX on (b) (6) Six days later, he had a UTI with a fever of 106. He received IV fluids, ceftriaxone IV, paracetamol and oral amoxicillin. The incident resolved (b) (6) The patient was withdrawn from study at the request of the Applicant. The Applicant classified this case as a UTI and assessed it as not related to study treatment, but possibly be related to administration procedure or the patient's concurrent medical condition.

Clinical Reviewer's Comment*: This reviewer finds that with a fever of 106, this event is more consistent with pyelonephritis than a UTI as the patient had severe systemic symptoms. The reviewer agrees that the event is serious and finds it related to study drug administration.*

Clinical Reviewer's Comment*: Overall, most of the cases of pyelonephritis occurred in timeframes remote from administration of BOTOX. Only one case, Patient (b) (6) occurred 6 days after study treatment. Three of the cases occurred in patients receiving BOTOX 100 U and one in a subject who received 200 U. There is no discernible correlation with dose. Three of the cases occurred with the second treatment cycle of BOTOX, while one occurred in the first treatment cycle. There is no discernible pattern of pyelonephritis occurring with increasing number of cycles (up to four cycles) of study drug administration. Pyelonephritis is not likely related to BOTOX or its administration.*

8.5.5.7. Potential Distant Spread of Toxin

PDSOT, a known adverse event associated with BOTOX, is suspected when there is evidence of possible pharmacologic effect of the botulinum toxin at sites noncontiguous and distant from the site of injection.

The MedDRA preferred terms evaluated for PDSOT included the following Table 35

Table 35. MedDRA Preferred Terms Evaluated for PDSOT

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

Source: From Table 2-11 Summary of Clinical Safety (p. 36/55)
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PDSOT, potential distant spread of toxin

Given that for NDO the drug is injected directly into the detrusor muscle, and urinary retention could be an expected localized effect, urinary retention was not considered a PDSOT for this application. Pediatric patients with NDO usually perform CIC as well, therefore urinary retention is less likely to be a problem.

Seven patients experienced TEAEs which could be associated with PDSOT. The abbreviated narratives are as follows:

- Patient (b) (6) in study 191622-120: 14-year-old girl with NDO due to spina bifida and spinal dysraphism with tethered cord, and a history of detethering of the spinal cord twice, and a myelomeningocele resection, urinary retention, incontinence, vesicoureteral reflux, bilateral ureteral reimplantation, hydronephrosis, pyelonephritis, constipation, migraine. She received 200 U during Cycle 1 and experienced mild blurred vision 207 days after injection, which resolved spontaneously the same day.

Five patients experienced constipation in the study:

- Patient (b) (6): 8-year-old boy with spinal dysraphism and myelomeningocele, closure of the myelomeningocele and follow-up scar revision, constipation requiring transanal irrigation and right renal cyst. He received 100 U BOTOX in Cycle 1 and 233 days later experienced moderate constipation treated with Normacol which resolved 136 days later.
- Patient (b) (6): 5-year-old boy who entered study 191622-121 after completing the initial study. He suffered an incomplete spinal cord injury after a motor vehicle accident, had a subdural hematoma, neurogenic bladder and bowel, paraplegia, constipation, and vesicoureteral reflux and multiple neurosurgeries. He was on ducosate sodium for constipation and oxybutynin for neurogenic bladder, among other medications. He received 100 U in Cycle 2 and experienced constipation 38 days after BOTOX administration. The event resolved with macrogol and sennoside A+B.
- Patient (b) (6): 16-year-old girl who completed study 191622-120 and entered the extension study. She had spina bifida and NDO, hydrocephalus with a shunt, bilateral hydronephrosis, chronic kidney disease, recurrent UTIs, Arnold-Chiari malformation, constipation, epilepsy, hypertension, obesity, mood changes, and multiple neurosurgeries. She was on salbutamol, enemas, levetiracetam, amlodipine, nitrofurantoin, ciprofloxacin, cefalexin, paracetamol, oxybutynin and multiple vitamin supplements. She received 100 U BOTOX in Cycle 2 and 200 U in cycle 3. 180 days after receiving the 100 U dose, she experienced moderate constipation which was treated with fosfosoda and magnesium hydroxide and resolved the same day.
- Patient (b) (6): 11-year-old girl with spina bifida and spinal dysraphism who received 100 U BOTOX in Cycle 2 during the extension study. She was taking paracetamol, furazidin for UTI prophylaxis and oxybutynin. 75 days after BOTOX injection she developed mild constipation and was treated with macrogol and the event was ongoing.
- Patient (b) (6): 6-year-old girl who entered study 191622-121 after completing the first study. She had spina bifida and spinal dysraphism and NDO, hydrocephalus with a ventriculoperitoneal shunt, vesicoureteral reflux, and constipation. She was on lactulose for constipation, Akritoin, cefuroxime, cefixime, amoxicillin+clavulanate, sulfamethoxazole trimethoprim for UTIs and ibuprofen and acetylcysteine for upper respiratory tract infection. 121 days after receiving 100 U BOTOX in cycle 2, she experienced mild constipation. She was treated with lactulose and macrogol and the event was ongoing.

One patient had muscular weakness. Patient (b) (6): 15-year-old boy who completed study 191622-120 and entered the extension study. He had spina bifida and fecal incontinence, constipation, enemas, multiple neurosurgeries. He was taking alfuzocin, cholestyramine, oxybutynin and ciprofloxacin. He received 100 U in treatment cycle 2 and 200 U in treatment cycle 3. He had muscular weakness 127 days after injection. No treatment was administered and the event was ongoing. The subject discontinued the study early as he was unable to return to the exit visit.

None of these events were assessed by the investigators or Applicant as related to distant spread of toxin.

Clinical Reviewer's Comment*: This reviewer agrees that the timing of the adverse event in relation to injection of BOTOX is inconsistent with BOTOX pharmacology and does not support distant spread of toxin (DSOT). Further, constipation was a pre-existing condition in four of the five patients experiencing this event during the study. The event was mild or moderate and resolved for most patients, making the association with BOTOX less likely.*

8.5.6. COA Analyses Informing Safety/Tolerability

The studies incorporated two PROs, the modified TBS and PinQ. These instruments were used to evaluate efficacy, with questions centered on how many patients leaked urine and questions related to quality of life. There were no questions which evaluated safety or tolerability of the treatment.

8.5.7. Safety Analyses by Demographic Subgroups

The Applicant asserts there were no differences in TEAEs when assessed by the following subgroups:

- Age ≥5 to <12 versus ≥12 to ≤17; overall rates 56.9% (33/58) versus 60.0% (33/55)
- Sex male versus female; overall rates 56.9% (37/65) versus 60.4% (29/48)
- Race Caucasian versus non-Caucasian—no meaningful conclusion could be drawn due to the fact that there were only 28 non-Caucasian patients, compared with 85 Caucasian patients.
- Etiology of NDO: spinal dysraphism versus spinal cord injury; 56.6% (56/99) versus 76.9% (10/13).
- Region North America versus European Union; 51.1% (24/47) versus 63.6% (42/66). Bacteriuria and UTI rates were lower in North America compared with the European Union (2.1% and 14.9% respectively).
- Type of Anesthesia: general versus no general anesthesia: In study 191622-120 there were more TEAEs within the first 12 weeks among those receiving general anesthesia 62.1%(54/87) versus 44.0% (11/25). The Applicant states that the only event that could be related to general anesthesia was vomiting, which only occurred in 3.4% of patients in the 100 U dose group. The Applicant concludes the TEAEs were likely not related to method of anesthesia.
- Baseline Anticholinergic Use: yes versus no: 53.3% (32/60) versus 64.2% (34/53). There were slightly lower TEAEs within the first 12 weeks in patients who continued anticholinergic use during the study.

Clinical Reviewer's Comment*: This reviewer queried the safety database and confirmed no differences in TEAEs by any of the above subgroups. As the number of treatment cycles increases, there are successively smaller sample sizes in each group, precluding meaningful analysis of differences.*

8.5.8. Specific Safety Studies/Clinical Trials

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

8.5.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The carcinogenic potential of BOTOX has not been evaluated.

Human Reproduction and Pregnancy

Females of childbearing potential who were sexually active were required to use adequate contraception during the study. These options included oral, transdermal, vaginal ring, injectable and implantable contraceptives, male condoms or female barrier methods with intravaginal spermicide, intrauterine device or intrauterine systems, sterilization or abstinence. Urine pregnancy testing was performed on site during Studies 191622-120 and 191622-121. There were no pregnancies reported in either study.

Pediatrics and Assessment of Effects on Growth

As expected in a pediatric population, patients experienced an increase in body weight during the study period.

Table 36. Weight Increase by Dose Group and Cycle

Treatment Cycle	BOTOX 50 U n/N (%)	BOTOX 100 U n/N (%)	BOTOX 200 U n/N (%)
Cycle 1	14/31 (45.2)	11/38 (28.9)	11/24 (45.8)
Cycle 2	3/8 (37.5)	29/42 (69.0)	26/35 (74.3)
Cycle 3	1/4 (25)	7/15 (46.7)	21/28 (75.0)
Cycle 4	1/1 (100)	1/3 (33.3)	2/2 (100)

Adapted from study 191622-121 Clinical Study Report Table 14.3-12.1, Table 14.3-12.2, Table 14.3-12.3, Table 14.3-12.4

A few patients experienced a decrease in weight of $\geq$5%. Only one subject in the 100 U group experienced a decrease in weight in cycle 1, while two experienced a decrease in weight in the 100 U group and one in the 200 U group in cycle 2. In cycle 3 only one subject in the 200 U group lost weight. No patients lost weight in cycle 4.

Notably the number of patients with decrease in weight with additional cycles; however, there does not appear to be an adverse effect of BOTOX on body weight, nor differences between dose groups over time.

Also as expected in a pediatric population, patients experienced an increase in height during the study period. However, after cycle 1, once baseline height measurements were taken, there were few patients for whom height was measured even by week 12. Based on the few patients for whom height data are available, there do not appear to be differences between dose groups. Given the limited data, a true assessment of change in height cannot be performed.

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.

Subgroup Receiving Less Than Their Assigned Dose Due to the Weight Cap

The Applicant was asked to conduct a post hoc analysis to identify the most common adverse reactions in the subgroup of patients who received less than their assigned dose due to the 6 U/kg weight cap. The most adverse reactions are the same as identified in the studied dose groups; however, the frequency appears higher. This is likely due to the small number of patients in this group (N=10); therefore, the frequencies are not interpretable. It is expected that the frequency of these adverse events would be similar to that in the dose groups studied.

Table 37. Adverse Reactions Reported by ≥3% of BOTOX-Treated Pediatric Patients Within the First 12 Weeks After Intradetusor Injection of a Dose Other Than Their Assigned Dose Due to the Weight Cap

Adverse Reactions	Patients Who Received Less Than Their Assigned Dose (N=10) n (%)
Urinary tract infection	2 (20)
Bacteriuria	3 (30)
Hematuria	1 (10)

Source: Table 31 in Module 1.11.3 Clinical Information Amendment SDN 436 BLA 103000

8.5.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant reported on the postmarketing experience with BOTOX. The postmarketing database was queried for reports received between January 1, 1990 and August 31, 2019 for pediatric patients with urologic indications selecting reports for the specific indication of NDO. Thirty-four reports containing 98 events were received. The most frequent AE preferred terms were UTI (14), drug ineffectiveness (5), drug ineffective for unapproved indication (5), overdose—patients received more than 8 U/kg—(8), therapeutic response decreased (5). There were four serious AEs, one of which was a UTI and two of which were device breakage (artificial urinary sphincter was perforated during procedure). The fourth event is not outlined in the application.

The Applicant also described safety information from published literature. Per a review conducted in September 2019, doses up to 360 U were used and no new safety findings were identified. Safety findings showed that UTI was the most common AE.

The Applicant further provided a 120-day safety update through August 2020. There were no new safety developments pertaining to the patients in the pediatric NDO program, nor new safety information from literature. There was one report of a 17-year-old male with a history of SCI at C6 who was treated for pediatric NDO with 300 U BOTOX for incontinence. The patient

experienced upper extremity weakness on an unknown date; the episode resolved 3 months later. There was a positive rechallenge. The Applicant concludes SCI patients may have a selective vulnerability in limb muscles associated with motor neuron damage adjacent to the spinal cord injury lesion.

This reviewer also conducted an additional literature search on the use of BOTOX in pediatric patients with NDO (Hopps and Kropp 2003; Verpoorten and Buyse 2008; Lehnert et al. 2012; Marte 2012; Kask et al. 2014; Greer et al. 2016; Scheepe et al. 2017; Hascoet et al. 2018; Peeraully et al. 2019). Some studies included patients with other urinary dysfunction that could not be attributed to NDO. All articles included a small number of patients (17 to 53). Doses of BOTOX used were up to 500 U. The most commonly reported AE in the articles was UTI. One article reported on urinary retention on a subject with NDO who was not performing CIC and one similarly noted a child with difficulty initiating voiding after injection. Other adverse events included painful penile sensation and mild lower abdominal pain. One child who was on daily aspirin had hematuria. These articles did not reveal any new safety concerns.

Clinical Reviewer's Comment*: the postmarket experience from the reported safety database and from literature searches did not reveal any new safety concerns for BOTOX in pediatric NDO.*

Expectations on Safety in the Postmarket Setting

Based on the safety data presented in the application as well as that from the Applicant's postmarket databases and the literature, expectations in postmarket setting of BOTOX in the pediatric NDO population reasonably include AEs of UTI (less likely pyelonephritis), bacteriuria and hematuria. This reviewer expects there may be some instances of progression of renal dysfunction if the drug does not work in some patients, so there may be instances of vesicoureteral reflux and hydronephrosis. There are expected to be few instances of urinary retention as most patients will be performing CIC.

8.5.11. Integrated Assessment of Safety

- The pediatric NDO BOTOX safety database is adequate for evaluation.
- There were no deaths reported during the studies.
- The most commonly reported TEAEs were UTI and bacteriuria, as expected based on the underlying condition. Rates of hematuria were very low, as were rates of hydronephrosis, vesicoureteral reflux and pyelonephritis.
- There were no differences in safety by subgroup (age, sex, race, etiology of NDO, region of the world, anesthesia or baseline anticholinergic use).
- There was also no evidence of DSOT in the clinical studies; PDSOT remains a labeled concern, especially since a recent postmarket report noted upper extremity weakness in a pediatric patient with SCI who received 300 U BOTOX (higher than the approved dose).
- Though there was a small number of analyzable samples for BABS, there does not appear to be any impact of immunogenicity on subject safety.

- There was no identifiable dose relationship for TEAEs or any other safety concern among the three BOTOX treatment groups.
- There was also no identifiable change in the safety profile with repeated treatments, though patient numbers in the third and fourth cycles were markedly lower than in the first two cycles.
- Similar adverse reactions including UTI, bacteriuria and hematuria were seen in pediatric patients dosed at BOTOX 6 U/Kg body weight.
- Queries of postmarket safety database queries and literature did not reveal any new safety concerns.

8.6. Statistical Issues

The safety analysis was based on the safety population and the number and percentage of patients who have AEs, TEAEs, STEAEs in each treatment group were summarized. Vital sign and laboratory parameter changes from baseline were also described by treatment group. No subgroup analyses were done, except for BABs as requested by the FDA during the review. No formal hypothesis testing was done. Therefore, there were no statistical issues with the safety analysis, except that there were so few patients included in the fourth treatment cycle, a meaningful conclusion could not be drawn from that cycle.

8.7. Conclusions and Recommendations

BOTOX for the treatment of pediatric NDO in children ages 5 to 17 appears safe at the three doses (50 U, 100 U and 200 U) studied, with no difference in the safety profile between the doses. Safety appears stable with repeated treatments, though few patients had as many as four cycles of treatment. Specific to this indication, labeling will include UTI, bacteriuria, and hematuria. Similar adverse reactions including UTI, bacteriuria and hematuria were seen in pediatric patients dosed at BOTOX 6 U/Kg body weight. Specific to BOTOX, known labelled safety concerns remain for PDSOT and immunogenicity.

Recommendation

BOTOX 200 U dose is recommended for approval for pediatric patients 5 to 17 years of age with NDO. Pediatric patients with NDO, who are less than 34 Kg in weight, can be dosed at BOTOX 6 U/Kg body weight.

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting nor were there other external consultations for this application.

10. Pediatrics

Consultation to the Division of Pediatric and Maternal Health (DPMH) was made for their assessment of the relative benefit-risk of the use of BOTOX in treating the youngest patients in the study, ages 5 to 17, as the original planned age for inclusion was 10 but was subsequently lowered due to difficulty with enrollment. Additionally, DPMH was asked to opine on the benefit-risk of different doses for the intended population.

DPMH noted that patients with congenital neural tube defects have shown evidence of renal injury, dilatation of the upper urinary tracts, and urinary retention on an average by three years of age, but this can occur as early as the first 6 months of life. If the neurogenic bladder sphincter dysfunction is left untreated, up to 58% of children show progressive deterioration in renal function by the age of three years. There are no appreciable maturational differences in bladder function between patients aged 5 to 7 compared with those 8 and older. DPMH opined that BOTOX offers an important therapeutic option by delaying or preventing the need for urinary diversion or bladder augmentation in children 5 to 7 years of age. The division further found that Studies 191622-120 and 191622-121 did not find any unique trends in efficacy or concerning differences in safety in patients 5 to 7 years old compared with those aged 8 and older. DPMH found the drug to be equally safe and effective at all doses and deferred to the clinical review division regarding which dose to approve.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed revisions to the BOTOX prescribing information (PI) and MG. DMEPA did not identify any vulnerabilities within the MG however, identified areas for proposed revisions to the BOTOX PI where additional information should be added, or information should be revised in order to promote the safe use of the product. See Table 38 for the identified issues, rationale for DMEPA's concern and recommendations.

As part of the review, DMEPA considered whether the proposed revisions to the PI and MG would require revisions to the carton labeling or container label to ensure consistency and decrease risk of confusion and medication errors. DMEPA noted that the proposed changes do not require changes to the strength, dosage form, route of administration, or packaging configuration. Therefore, DMEPA finds the currently marketed carton labeling and container label supports the dosage and administration for the proposed expanded indication and patient population.

Table 38. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology

Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information – Section 2 Dosage and Administration		
The following error prone abbreviations and symbols, IV, ≤, <, ≥, >, and U are used.	The use of error prone abbreviations and symbols is not in alignment with current safe medication practices.	We recommend IV, ≤, <, ≥, >, and U be converted to their intended meanings.
Not all numeric digits are followed by a space when the units of measure are displayed.	May increase the risk for misinterpretation of "U" as a "0", which could lead to wrong dose medication errors.	We recommend placing a space between all numeric digits and their respective unit of measure (for example, revise 100U to read 100 Units).
In section 2.4, description of anesthetic use, the lower bound of the age range for the proposed indication is not present in the statement '(b) (4) years of age."	May increase the risk for use of general anesthesia in an unapproved population.	We recommend revising '(b) (4) years of age" to read "in patients 5 years to less than 12 years of age."
The maximum dose statement '(b) (4) " can be improved for clarity.	May increase the risk for dosing confusion.	We recommend splitting the maximum dose statement and placing it with the appropriate weight-based reconstitution instructions to read: "if patient's body weight is greater than or equal to 34 kg, the recommended dose is 200 Units of BOTOX per treatment" and "If patient's body weight is less than 34 kg, the recommended dose is weight-based, not to exceed 6 Units/kg body weight (refer to Table 2)."
The column heading titled 'Final dose of BOTOX in doing syringe' within Table 2 contains a footnote '**' that states (b) (4) However, it is unclear whether this footnote is necessary.	The final dose of BOTOX in dosing syringe (in Units) is a function of the volume of BOTOX (mL) for the weight range and the concentration of BOTOX. Thus, it is unclear how the final dose of BOTOX in the dosing syringe is (b) (4)	We recommend deleting the notation (b) (4) or providing additional clarification.

Source: The DUOG Review Team

12. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are required for this application.

13. Postmarketing Requirements and Commitment

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

14. Division Director (DHOT) Comments

15. Division Director (OCP) Comments

16. Division Director (OB) Comments

17. Division Director (Clinical) Comments

The population of NDO children inadequately managed by anticholingeric medications currently has no approved medical treatment options.

I concur with the Cross-Discipline Team Leader's recommendation to approve the BOTOX 200 U dose or BOTOX 6U/kg for children weighing less than 34 kilograms. Regarding efficacy, all three doses (50U, 100U, and 200U) reduced similarly the frequency of day time urinary incontinence episodes (primary endpoint) and other clinical and urodynamic endpoints. However, compared

to the 50U and 100U, the 200U dose group offered a greater reduction in the maximal detrusor pressure (PdetMax) in the storage phase as well as greater proportion of patients with the PdetMax <40 cm^2. No unexpected safety findings were noted in this pediatric NDO program. The safety profile, both qualitatively and quantitatively, appears to be similar across the 3 dose groups. These adverse findings could be adequately managed with labeling. Overall, the benefit-risk balance favors the approval of the 200U dose. Because the prespecified dose-limit in the pediatric NDO studies was 6U/kg, lighter weight children did not receive the 200U dose. Post hoc analyses of children receiving the maximal dose of 6U/kg, but with a total of less than 200U, indicate similar efficacy and safety findings. Thus, the approved dose of 6U/kg provides a much-treated a treatment option for children weighing less than 34 kilograms and who are inadequately managed by anticholinergic medication.

18. Appendices

18.1. References

Allergan, 2012, Prescribing Information: SANCTURA (trospium chloride) tablets, FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021595s009lbl.pdf.

Allergan, 2020, Prescribing Information: BOTOX (onabotulinumtoxinA) for injection, FDA, accessed August 4, 2020, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103000s5317lbl.pdf.

Astellas Pharma US, 2020, Prescribing Information: VESICARE LS (solifenacin succinate) oral suspension, FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209529s000lbl.pdf.

Baskin, LS, 2020, Myelomeningocele (spina bifida): Urinary tract complications, UpToDate,

Cetinel, B, E Kocjancic, and C Demirdag, 2016, Augmentation cystoplasty in neurogenic bladder, Investig Clin Urol, 57(5):316-323.

Game, X, P Mouracade, E Chartier-Kastler, E Viehweger, R Moog, G Amarenco, P Denys, M De Seze, F Haab, G Karsenty, J Kerdraon, B Perrouin-Verbe, A Ruffion, JM Soler, and C Saussine, 2009, Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review, J Pediatr Urol, 5(3):156-164.

Greer, T, J Abbott, W Breytenbach, D McGuane, A Barker, J Khosa, and N Samnakay, 2016, Ten years of experience with intravesical and intrasphincteric onabotulinumtoxinA in children, J Pediatr Urol, 12(2):94 e91-96.

Hascoet, J, B Peyronnet, V Forin, M Baron, G Capon, T Prudhomme, C Allenet, S Tournier, C Maurin, JN Cornu, O Bouali, M Peycelon, A Arnaud, M Renaux-Petel, A Liard, G Karsenty, A Manunta, and X Game, 2018, Intradetrusor Injections of Botulinum Toxin Type A in Children With Spina Bifida: A Multicenter Study, Urology, 116:161-167.

Hopps, CV and KA Kropp, 2003, Preservation of renal function in children with myelomeningocele managed with basic newborn evaluation and close followup, J Urol, 169(1):305-308.

Kask, M, R Rintala, and S Taskinen, 2014, Effect of onabotulinumtoxinA treatment on symptoms and urodynamic findings in pediatric neurogenic bladder, J Pediatr Urol, 10(2):280-283.

Lehnert, T, M Weisser, H Till, and U Rolle, 2012, The effects of long-term medical treatment combined with clean intermittent catheterization in children with neurogenic detrusor overactivity, Int Urol Nephrol, 44(2):335-341.

Marte, A, 2012, Onabotulinumtoxin A for treating overactive/poor compliant bladders in children and adolescents with neurogenic bladder secondary to myelomeningocele, Toxins (Basel), 5(1):16-24.

Ortho-McNeil-Janssen Pharmaceuticals, 2012, Prescribing Information: DITROPAN (oxybutynin chloride) Tablets, FDA, accessed August 4, 2020, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017577s038lbl.pdf.

Ortho-McNeil Pharmaceuticals, 2008, Prescribing Information: DITROPAN (oxybutynin chloride) Tablets and Syrup, FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017577s034,018211s017,020897s018lbl.pdf.

Peeraully, R, C Lam, N Mediratta, R Patel, A Williams, M Shenoy, and N Fraser, 2019, Intradetrusor injection of botulinum toxin A in children: a 10-year single centre experience, Int Urol Nephrol, 51(8):1321-1327.

Pfizer Labs, 2017, Prescribing Information: TOVIAZ (fesoterodine fumarate) extended-release tablets, FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022030s014lbl.pdf.

Pharmacia & Upjohn Co, 2012, Prescribing Information: DETROL (tolterodine tartrate) Tablets, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020771s028lbl.pdf.

Pharmacia & Upjohn Co, 2018, Prescribing Information: DETROL (tolterodine tartrate) LA capsules, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021228s023lbl.pdf.

Scheepe, JR, BF Blok, and LA t Hoen, 2017, Applicability of botulinum toxin type A in paediatric neurogenic bladder management, Curr Opin Urol, 27(1):14-19.

Tekgul, S, H Riedmiller, E Gerharz, R Hoebeke, JM Nijman, and RR Stein, 2011, Guidelines on Paediatric Urology, European Association of Urology (EUA) Guidelines, 114

Verpoorten, C and GM Buyse, 2008, The neurogenic bladder: medical treatment, Pediatr Nephrol, 23(5):717-725.

Warner Chilcott, 2012, Prescribing Information: ENABLEX (darifenacin) extended-release tablets, FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021513s010lbl.pdf.

18.2. Financial Disclosure

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)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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