

# OnabotulinumtoxinA for the treatment of neurogenic detrusor overactivity in children

Paul F. Austin MD<sup>1</sup>  | Israel Franco MD<sup>2</sup>  | Eric Dobremez MD, PhD<sup>3</sup> |  
 Pawel Kroll MD, PhD<sup>4</sup> | Wilson Titanji PhD<sup>5</sup> | Till Geib PhD<sup>5</sup> |  
 Brenda Jenkins BS<sup>5</sup> | Piet B. Hoebeke MD<sup>6</sup>

<sup>1</sup>Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA

<sup>2</sup>Yale New Haven Children's Hospital, New Haven, Connecticut, USA

<sup>3</sup>Hôpital Pellegrin Enfants, Bordeaux, France

<sup>4</sup>Neuro-urology Unit, Paediatric Urology Clinic, Poznań, Poland

<sup>5</sup>Allergan, an AbbVie company, Irvine, California, USA

<sup>6</sup>Ghent University Hospital, Ghent, Belgium

## Correspondence

Paul F. Austin, MD, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin St, Houston, TX 77030, USA.  
 Email: [pfaustin@texaschildrens.org](mailto:pfaustin@texaschildrens.org)

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## Abstract

**Aims:** This study evaluated whether one (or more) of three doses of onabotulinumtoxinA were safe and effective to treat neurogenic detrusor overactivity (NDO) in children.

**Methods:** This was a 48-week prospective, multicenter, randomized, double-blind study in children (aged 5–17 years) with NDO and urinary incontinence (UI) receiving one onabotulinumtoxinA treatment (50, 100, or 200 U; not to exceed 6 U/kg). Primary endpoint: change from baseline in daytime UI episodes. Secondary endpoints: change from baseline in urine volume at first morning catheterization, urodynamic measures, and positive response on the treatment benefit scale. Safety was also assessed.

**Results:** There was a similar reduction in urinary incontinence from baseline to Week 6 for all doses (−1.3 episodes/day). Most patients reported positive responses on the treatment benefit scale (75.0%–80.5%). From baseline to Week 6, increases were observed in urine volume at first morning clean intermittent catheterization (50 U, 21.9 ml; 100 U, 34.9 ml; 200 U, 87.5 ml;  $p = 0.0055$ , 200 U vs. 50 U) and in maximum cystometric capacity (range 48.6–63.6 ml) and decreases in maximum detrusor pressure during the storage phase (50 U, −12.9; 100 U, −20.1; 200 U, −27.3 cmH<sub>2</sub>O;  $p = 0.0157$ , 200 U vs. 50 U). The proportion of patients experiencing involuntary detrusor contractions dropped from baseline (50 U, 94.4%; 100 U, 88.1%; 200 U, 92.6%) to Week 6 (50 U, 61.8%; 100 U, 44.7%; 200 U, 46.4%). Safety was similar across doses; urinary tract infection was most frequent.

**Conclusions:** OnabotulinumtoxinA was well tolerated and effective for the treatment of NDO in children; 200 U showed greater efficacy in reducing bladder pressure and increasing bladder capacity.

## KEYWORDS

botulinum toxins, neurogenic, pediatrics, Type A, urinary bladder

## 1 | INTRODUCTION

Neurogenic detrusor overactivity (NDO) is a condition characterized by involuntary detrusor contractions (IDCs) during the bladder filling phase that can result in urinary incontinence (UI).<sup>1</sup> Any neurological condition that impacts the brain or spinal cord, resulting in the interruption of the signaling pathways that control bladder function—for example, spinal cord injury, multiple sclerosis, or spinal dysraphism—may lead to NDO.<sup>2,3</sup> Types of relevant spinal dysraphism include myelomeningocele (MMC), spina bifida occulta, split cord malformation (diastematomyelia), spinal cord lipoma (lipomyelomeningocele), dermal sinus tract, and tethered spinal cord.<sup>4,5</sup> MMC is the most common neurological disorder responsible for bladder dysfunction in pediatric patients, with traumatic and neoplastic spinal cord lesions being less frequent.<sup>6–8</sup>

NDO can lead to elevated bladder pressures and, if not adequately managed with standard treatment, may require augmentation cystoplasty to prevent renal damage.<sup>9</sup> The primary goal of NDO treatment is to attain and maintain safe bladder storage pressures to avoid kidney damage. A detrusor pressure of 40 cmH<sub>2</sub>O has been cited as a critical threshold above which patients may be at increased risk for upper urinary tract dysfunction resulting in renal damage.<sup>10</sup>

Joint guidelines from the European Society for Paediatric Urology and the European Association of Urology suggest that in children with NDO, starting the use of clean intermittent catheterization (CIC) early can help minimize upper tract changes, provide better bladder protection, and lower UI rates.<sup>11</sup> Similarly, the International Children's Continence Society recommends pharmacotherapy with oral anticholinergic medications in conjunction with CIC.<sup>12</sup> However, 10%–15% of these patients fail to respond to these treatments, and side effects may be limiting.<sup>13–15</sup>

OnabotulinumtoxinA 200 U is a well tolerated and effective treatment option approved for adults with UI due to NDO inadequately controlled with anticholinergic therapy.<sup>16</sup> Although onabotulinumtoxinA is not currently approved for children with NDO, several published studies demonstrated positive efficacy with acceptable safety in this population at doses up to 360 U. A systematic literature review demonstrated that after onabotulinumtoxinA treatment, 32%–100% of pediatric patients were continent, with maximum detrusor pressure (MDP) reductions of 32% to 54%, often below the 40 cmH<sub>2</sub>O threshold.<sup>17</sup> However, to date, there is no consensus as to what dose has optimal efficacy and safety, and currently available information is inadequate to guide dosing decisions for the use of

onabotulinumtoxinA in this population. The goal of the current program was to fill this gap and determine if one or more of three onabotulinumtoxinA doses (50, 100, and 200 U; not to exceed 6 U/kg) were safe and effective for the treatment of NDO in children inadequately managed with anticholinergic therapy.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This was a Phase 3, prospective, international, multicenter, randomized, double-blind study with a maximum duration of 48 weeks ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT01852045). Overall, 31 sites in 8 countries (United States, Canada, Belgium, Czech Republic, France, Italy, Poland, and Turkey) enrolled and treated patients (July 11, 2013 to October 11, 2018).

### 2.2 | Study population

Children (5–17 years) with NDO due to spinal dysraphism, transverse myelitis, or spinal cord injury, based on the presence of an IDC during urodynamics, were included. Patients were inadequately managed with anticholinergic agents (i.e., were still incontinent, experiencing intolerable side effects, or unwilling to continue the medication) and were regularly using CIC ( $\geq 3$  times/day for  $\geq 3$  months before screening). Patients must have had  $\geq 4$  daytime UI episodes over a 2-day diary completed during screening. “Daytime” was defined as the time between waking up to start the day and going to bed to sleep for the night.

Patients were excluded who had cerebral palsy, spinal cord surgery within 6 months of screening, or previous/current botulinum toxin therapy of any serotype for any urological condition. Patients could discontinue their anticholinergics within 7 days of the start of the screening, or continue at a stable dose throughout the study.

### 2.3 | Study treatment

Patients were centrally randomized through an interactive web response system in a 1:1:1 ratio to one treatment of onabotulinumtoxinA 50, 100, or 200 U (not to exceed 6 U/kg). While nonclinical studies support dosing up to 8 U/kg, a conservative approach of 6 U/kg was taken due to the pediatric population being studied. The 50 U low dose was included in lieu of a placebo control arm (owing to ethical concerns in children).

Patients, physicians, and study staff were blinded to treatment. Medication was reconstituted by an independent drug reconstitutor not associated or involved with the study patients' care or assessments.

Patients received prophylactic antibiotic treatment. OnabotulinumtoxinA was delivered via cystoscopy as 20 intradetrusor injections of 0.5 ml excluding the trigone, under general anesthesia/conscious sedation or instillation of local anesthetic (only allowed for patients >12 years of age).

Patients had posttreatment follow-up clinic visits at Weeks 2, 6, and 12, then alternating telephone and clinic follow-up visits every 6 weeks up to 48 weeks.

Patients could request onabotulinumtoxinA retreatment  $\geq 12$  weeks after the first treatment, with the retreatment administered in a long-term extension study ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT01852058). Retreatments required  $\geq 2$  daytime UI episodes over a 2-day bladder diary. If patients did not request/qualify for retreatment during the 48 weeks of the study, they exited the study and could enroll in the extension study.

This study was conducted in conformance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, or the laws/regulations of the country in which the research was conducted. Assent was obtained from the patients, and informed consent was provided by parents/guardians.

## 2.4 | Key efficacy endpoints

### 2.4.1 | Primary endpoint

Change from baseline in the daily average frequency of daytime UI episodes/day (from a 2-day bladder diary). The primary time point was Week 6. This primary endpoint was selected owing to regulatory requirements that the pediatric study mirror the NDO Phase 3 pivotal trials of onabotulinumtoxinA in adults.

### 2.4.2 | Key secondary endpoints

Change from baseline in urine volume at first morning catheterization (collected "upon waking for the day") and urodynamic measures of change from baseline in MDP (cmH<sub>2</sub>O) during the storage phase.

### 2.4.3 | Other secondary endpoints

Percentage of patients experiencing IDC, change from baseline in maximum cystometric capacity (MCC), the

proportion of patients with positive treatment response on the modified treatment benefit scale (TBS), and duration of effect (time to patient request for retreatment). The TBS is a single-item measure of the patient's/parent's perception of posttreatment benefit (1 = greatly improved; 2 = improved; 3 = not changed; 4 = worsened).<sup>18</sup> A positive response was defined as the patient's condition had "greatly improved" or "improved."

Urodynamic testing was administered at baseline and Week 6 and performed according to the standards of good clinical practice as set forth by the International Continence Society and the International Children's Continence Society.<sup>19–21</sup> An independent central reviewer provided a quality review and validation of urodynamic tracings and results for analysis.

## 2.5 | Safety

Safety analyses included all patients who received the study drug based on actual treatment received, with patients allocated to the nearest dose group. As patients could request retreatment and move to the extension study from Week 12 onward, adverse events (AEs) and serious AEs (SAEs) were presented over the initial 12 weeks to allow for meaningful comparison across treatment groups, as well as over the entire treatment cycle. Urinary tract infection (UTI) was symptomatic and, in the investigator's opinion, required treatment.

## 2.6 | Statistical analysis

Assuming 30 patients/group and a two-sided Type I error rate of 0.05, and using a range of standard deviations (2–4) based on the 200 U dose group in the adult Phase 3 NDO studies, the confidence interval approach to determining sample size was used to show that the widths of the confidence intervals obtained for the difference between treatment groups in the primary efficacy variable were clinically acceptable. Thirty-four patients/group were planned for enrollment in this study (accounting for a potential attrition rate of 10% by Week 6).

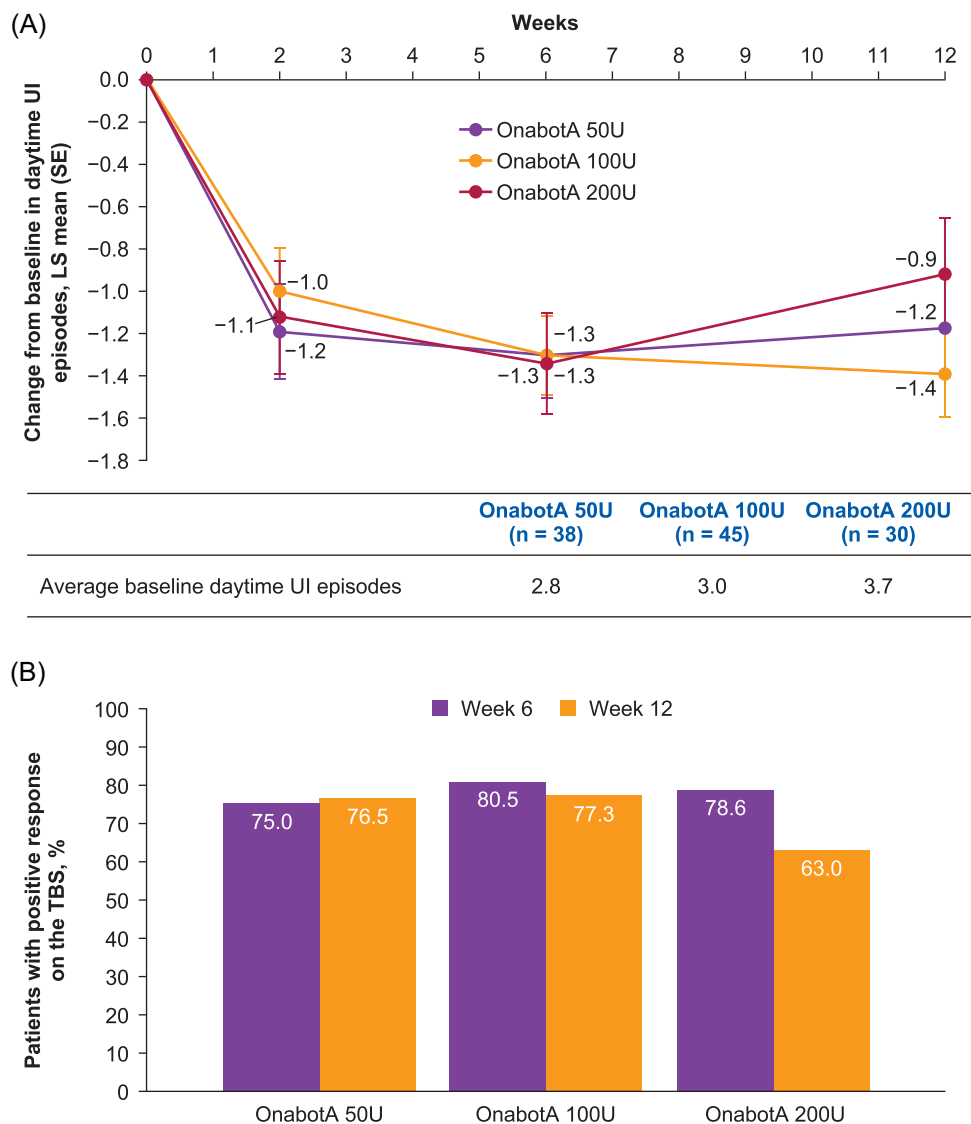
Efficacy data were analyzed using the modified intent-to-treat population consisting of all randomized patients who received treatment. Patients were analyzed using their randomized treatment assignment except for those who, owing to the 6 U/kg maximum, received a lower dose than assigned and were assigned to the nearest dose group based on the dose actually received. The lowest dose (50 U) group was used as the comparator in all statistical testing.

The last-observation-carried-forward approach was used to impute missing daily average frequency of

**TABLE 1** Baseline demographic and disease characteristics

	<b>OnabotA 50 U (n = 38)</b>	<b>OnabotA 100 U (n = 45)</b>	<b>OnabotA 200 U (n = 30)</b>	<b>Total (N = 113)</b>
Age, years, mean $\pm$ SD	11.4 $\pm$ 3.5	10.8 $\pm$ 3.3	11.9 $\pm$ 3.1	11.3 $\pm$ 3.3
Male, n (%)	20 (52.6)	30 (66.7)	15 (50.0)	65 (57.5)
White, n (%)	29 (76.3)	34 (75.6)	22 (73.3)	85 (75.2)
Weight, kg, mean $\pm$ SD	41.9 $\pm$ 18.1	40.1 $\pm$ 23.5	46.9 $\pm$ 15.3	42.5 $\pm$ 19.8
Neurological 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)	13 (11.5)
Transverse myelitis	0 (0.0)	0 (0.0)	1 (3.3)	1 (0.9)

Abbreviation: OnabotA, onabotulinumtoxinA; SD, standard deviation.

**FIGURE 1** (A) LS mean change from baseline overtime in daytime UI episodes and (B) proportion of patients with a positive response on the TBS following onabotA treatment. Positive response was recorded as patients reporting their condition was “improved” or “greatly improved.” Error bars reflect standard error. LS, least squares; OnabotA, onabotulinumtoxinA; TBS, treatment benefit scale; UI, urinary incontinence

daytime urinary incontinence episodes, up to Week 6. Pairwise treatment differences at each visit were obtained using an analysis of covariance model for continuous variables and the Cochran–Mantel–Haenszel method for categorical variables, controlling for baseline, age (<12 years or  $\geq$ 12 years), baseline daytime UI episodes (a total of  $\leq$ 6 episodes or  $>$ 6 episodes over the 2-day diary), and anticholinergic therapy use (no/yes) at baseline. The Kaplan–Meier method was used to provide median estimates for time to event data.

All significance levels were two-sided, with  $p < 0.05$  indicating statistical significance. Analyses were conducted using SAS version 9.4 statistical software (SAS Institute Inc.).

### 3 | RESULTS

#### 3.1 | Baseline demographics and patient characteristics

Baseline demographic and disease characteristics are listed in Table 1. Spinal dysraphism was the primary cause of NDO.

Overall, 114 patients were enrolled and randomized; 100/114 (87.7%) completed the study (48 weeks completion or qualified for retreatment), and 14/114 (12.3%) discontinued the study early (Figure S1). In total, 113 patients received study medication; both the modified intent-to-treat and safety populations consisted of 38, 45,

and 30 patients in the 50, 100, and 200 U onabotulinumtoxinA treatment groups, respectively. Due to the 6 U/kg maximum, the number of patients who received 200 U was smaller as six patients were analyzed in one of the lower dose groups. Patients analyzed in the 200 U dose group received between 168 and 200 U, patients analyzed in the 100 U group received between 96 and 144 U, and patients analyzed in the 50 U group received between 50 and 72 U.

#### 3.2 | Efficacy

Improvements from baseline in the number of daytime UI episodes were observed in all dose groups (Figure 1A); each dose group resulted in statistically significant and clinically meaningful within-group reductions from baseline. There were no differences in daytime UI episodes for onabotulinumtoxinA 100 or 200 U compared with onabotulinumtoxinA 50 U ( $p = 0.9949$  and  $p = 0.9123$ , respectively).

After 6 weeks, the majority of patients in each group reported “great improvement” or “improvement” on the TBS (Figure 1B). The 100 and 200 U groups were not statistically significantly different from the 50 U group ( $p = 0.6884$  and  $p = 0.6112$ , respectively). Improvements were sustained to Week 12.

A dose-dependent increase in functional bladder capacity, measured by the volume at first morning catheterization recordings, was seen with escalating dosages of onabotulinumtoxinA (Figure 2). The adjusted mean change from

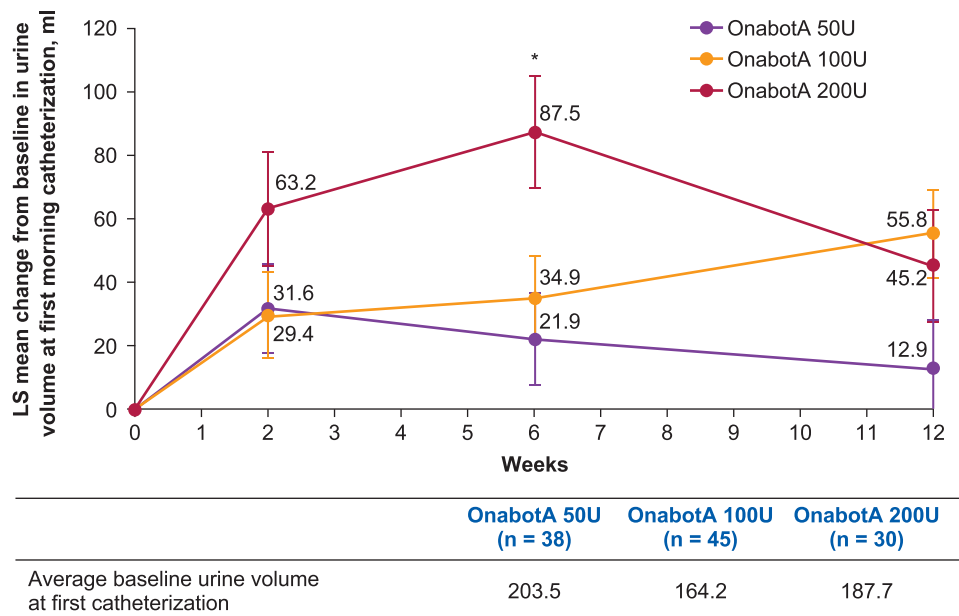
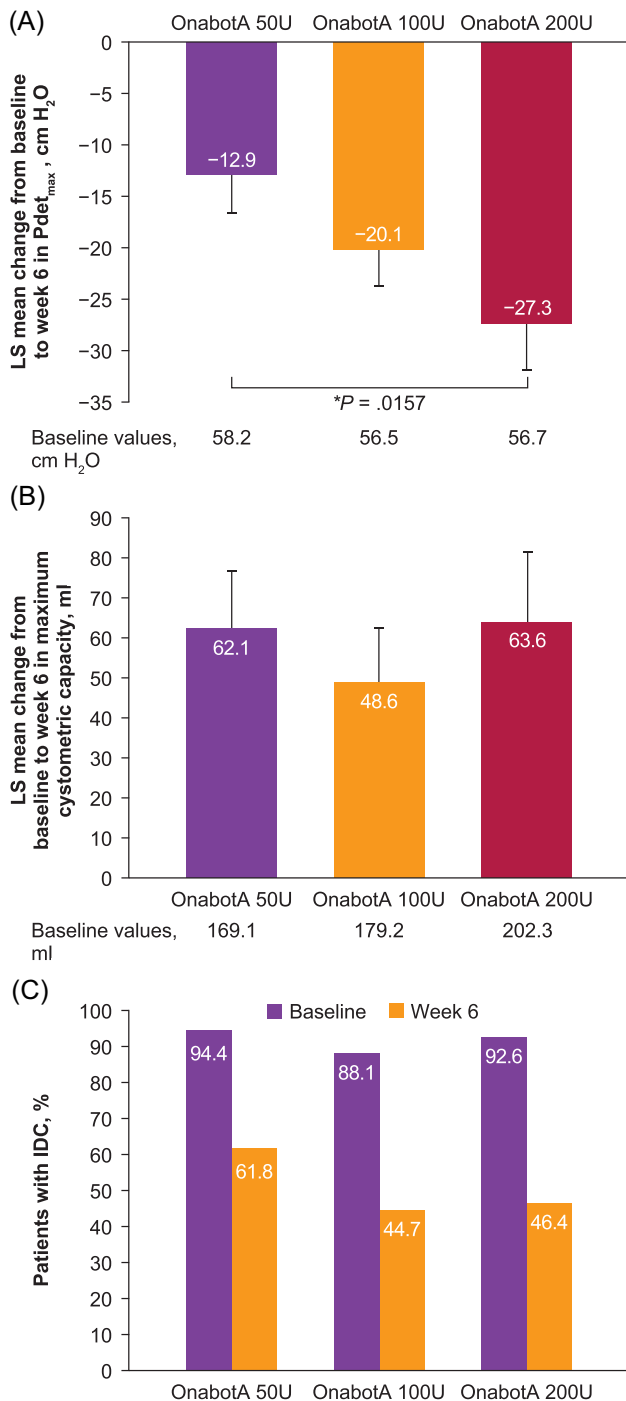


FIGURE 2 LS mean change from baseline in urine volume at first-morning catheterization overtime (weeks). \*Significant versus onabotA 50 U.  $p = 0.0055$ . Error bars reflect standard error. LS, least squares; OnabotA, onabotulinumtoxinA



**FIGURE 3** 3LS mean changes from baseline to Week 6 in (A)  $P_{det_{max}}$ , (B) MCC, and (C) proportion of patients with IDC.

\*Statistically significant versus 50 U. Error bars reflect standard error. IDC, involuntary detrusor contraction; LS, least squares; MCC, maximum cystometric pressure; OnabotA, onabotulinumtoxinA;  $P_{det_{max}}$ , largest decrease in maximum detrusor pressure during the storage phase

baseline at Week 6 was statistically significant and clinically meaningful for the 200 U versus 50 U doses ( $p = 0.0055$ ).

Furthermore, a significant improvement from baseline in urodynamic storage pressures was also seen with

increasing dosages of onabotulinumtoxinA, with the largest decrease in MDP during the storage phase ( $P_{det_{max}}$ ) seen in the 200 U arm when compared with 50 U ( $p = 0.0157$ ; Figure 3A).

There was an increase from baseline to Week 6 in MCC in all dose groups, with no significant differences between the doses (Figure 3B).

There was a reduction in all dose groups from baseline to Week 6 in the percentage of patients experiencing IDC, with a numerical trend favoring the 100 and 200 U groups (Figure 3C).

Duration of effect, based on median time for patients to request retreatment, was 30.6, 24.1, and 29.6 weeks in the 50, 100, and 200 U groups, respectively.

### 3.3 | Safety

The safety profile of onabotulinumtoxinA in this pediatric population was similar across doses. Over the entire study period, treatment-emergent AEs were reported in 71.1% to 76.7% of patients; SAEs in 6.7% to 10.5% of patients (Table S1). There were no deaths, cases of pyelonephritis, or evidence of distant spread of toxin in any treatment group. One patient in the 50 U group discontinued the study due to an AE; one event of cystitis was reported as serious. Over the first 12 weeks following onabotulinumtoxinA treatment, 47.4%–66.7% of patients experienced AEs (Table S1).

UTI was the most common AE reported, with no evident dose-dependent relationship (Table S1). Four incidences of UTI were classified as serious as these patients required hospitalization (50 U, 2/38 [5.3%]; 100 U, 2/45 [4.4%]). Most AEs of UTI occurred later than 2 weeks following treatment (Table 2). Annualized UTI event rates were calculated for the treatment period versus 6 months before treatment; no dose-related trend was seen, and there was no difference in the UTI event rate posttreatment compared with the 6 months before treatment (Table 2).

## 4 | DISCUSSION

A fixed dosing approach of onabotulinumtoxinA 50, 100, or 200 U (not to exceed 6 U/kg) was utilized in this study. While it is common for pediatric dosing to be based on U/kg, the fixed-dose approach for this study was based on the nonlinear relationship between age and bladder capacity. Although bladder capacity in children increases sharply during infancy and early childhood, the rate of increase tapers off substantially in children around the age of 4 years.<sup>22</sup> Considering the maximum

TABLE 2 Urinary tract infections by treatment interval

Interval after treatment	OnabotA 50 U (n = 38)	OnabotA 100 U (n = 45)	OnabotA 200 U (n = 30)	Total (N = 113)		
2 weeks	1 (2.6)	3 (6.7)	0	4 (3.5)		
12 weeks	7 (18.4)	13 (28.9)	2 (6.7)	22 (19.5)		
Entire period	11 (28.9)	15 (33.3)	7 (23.3)	33 (29.2)		
Annualized rates of UTI <sup>a</sup>						
	Period within 6 months before screening			Full treatment period		
	OnabotA 50 U (n = 38)	OnabotA 100 U (n = 45)	OnabotA 200 U (n = 30)	OnabotA 50 U (n = 38)	OnabotA 100 U (n = 45)	OnabotA 200 U (n = 30)
n (%)	7 (18.4)	10 (22.2)	7 (23.3)	11 (28.9)	15 (33.3)	7 (23.3)
Total UTI event rate	9	22	14	14	24	9
Total patient years	19.0	22.5	15.0	21.0	23.8	15.9
UTI event rate per patient year	0.47	0.98	0.93	0.67	1.01	0.57

Abbreviations: OnabotA, onabotulinumtoxinA; UTI, urinary tract infection.

<sup>a</sup>The UTI annualized rates (i.e., UTI events per patient year) were calculated by the sum of all of the patient's UTI events experienced during the treatment period (or 6 months prior) divided by the sum of all the patient's duration in years during the treatment period (or 6 months prior).

recommended dose for onabotulinumtoxinA spasticity indications is, in general, higher than that for urological indications (e.g., 300 U for adult spasticity vs. 200 U for adult NDO), the 6 U/kg safety cap was selected for the pediatric doses to reflect this experience (e.g., 8 U/kg for spasticity and 6 U/kg cap for NDO). This study in a vulnerable pediatric population with poorly controlled NDO was not placebo-controlled owing to ethical concerns. While this may be considered a limitation, a 50 U low-dose arm was included in lieu of a placebo group in anticipation of this dose showing significantly reduced efficacy when compared with higher doses. This was the case for several objective endpoints demonstrating reduced bladder pressure and increased bladder capacity; however, it was not true for the more subjective endpoints related to UI. Each dose of onabotulinumtoxinA (50, 100, and 200 U; not to exceed 6 U/kg) was well tolerated. As previous studies were mostly conducted using higher doses, it was surprising that all three doses demonstrated clinically significant improvements in UI in these children. No significant differences in UI reduction were seen between onabotulinumtoxinA 200 and 100 U versus 50 U, indicating similar treatment effects for each arm. This is supported by the finding that most patients across all dose groups gave positive responses on the TBS at Week 6, and duration of effect (time to request retreatment) was similar (approximately 6 months) in the three dose arms. As patient satisfaction and request for retreatment are mostly driven by the experience of UI,

the alignment of these analyses would be expected. Another limitation of this study is that collecting and interpreting incontinence episode data via a diary in children can be challenging, as many of these patients are in diapers and may be unable to perceive bladder fullness or leakage. In some patients, leakage would most likely be observed in undergarments or diapers only at the time of catheterization. Thus, changes in the frequency of incontinence between catheterizations may not be evident and collected in the diary for some patients, which may have contributed to the low (50 U), middle (100 U), and high doses (200 U) responding similarly for incontinence endpoints.

While the reduction in UI is important from a quality of life perspective, the primary goal in treating pediatric NDO patients is to attain and maintain safe bladder storage pressures and bladder capacities to prevent permanent damage to the bladder, ureters, and kidneys. Chronically raised bladder pressures are of great concern and have been shown to lead to renal dysfunction and even mortality.<sup>9,23,24</sup> Here, the 200 U dose of onabotulinumtoxinA showed clinically and statistically greater improvements versus 50 U in measures of Pdet<sub>max</sub>. With the ultimate goal to reduce bladder pressures as low and as close to that of a normal bladder as possible to avoid potential renal damage, a storage pressure of 40 cmH<sub>2</sub>O has been established as a critical threshold that patients should not exceed.<sup>10</sup> In this study, the 200 U dose demonstrated the most significant reduction in mean

detrusor pressure, to approximately 30 cmH<sub>2</sub>O, compared with the lower doses.

A dose–response relationship was also observed for volume at first morning void, which is the best indicator of functional bladder capacity because it represents the natural filling of the bladder over a long period of time (i.e., overnight). Here as well, the 200 U dose demonstrated a significantly greater improvement in volume versus the 50 U dose.

These findings were also supported by the observation that the number of patients experiencing IDCs dropped for each of the three dose groups from baseline to Week 6, with the 200 U dose arm showing a numerically larger decline than the 50 U arm.

It was not surprising that the most common AE was UTI; however, it is interesting that a dose–response trend was not seen and reassuring that onabotulinumtoxinA injections overall did not result in more UTIs than before treatment.

Based on the similar safety profile across the low, medium, and high dose groups, and the clinically important improvements seen in reducing detrusor pressure and increasing bladder capacity, it appears appropriate to treat pediatric patients with NDO with the approved adult onabotulinumtoxinA dose of 200 U (not to exceed 6 U/kg).

## 5 | CONCLUSIONS

OnabotulinumtoxinA 200 U (not to exceed 6 U/kg) is a well tolerated and effective treatment for children aged 5–17 years with signs and symptoms of NDO inadequately managed with anticholinergic therapy. While reductions in UI episodes were similar across doses, the 200 U dose demonstrated a statistically and clinically significant greater improvement in Pdet<sub>max</sub>, as well as increases in functional bladder capacity measured by the first morning catheterization, versus the low dose of 50 U. A long-term extension study is ongoing to evaluate the continued safety and efficacy following repeat treatment with onabotulinumtoxinA.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTERESTS

Dr. Austin has served as a consultant/advisor to Allergan, an AbbVie company. Dr. Franco has served as a

consultant/advisor to Allergan, an AbbVie company, and is chief science officer of FIAS Inc. (a software company) and chief science officer for Gogoband Inc. (a software and bedwetting device maker). Dr. Dobremez has served as a consultant for Allergan, an AbbVie company. Pawel Kroll has served as a study investigator for Allergan, an AbbVie company. Dr. Titanji, Dr. Geib, and Ms. Jenkins are employees of AbbVie, and may hold AbbVie stock. Dr. Hoebeke has served as a consultant for Allergan, an AbbVie company and Astellas.

## ORCID

Paul F. Austin  <https://orcid.org/0000-0003-3654-9524>

Israel Franco  <http://orcid.org/0000-0002-5675-873X>

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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