A Randomized Controlled Trial Evaluating Three Active Doses of OnabotulinumtoxinA for the Treatment of Neurogenic Detrusor Overactivity in Children

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Paul F. Austin has served as a consultant/advisor to Allergan plc.

Israel Franco has served as a consultant/advisor to Allergan plc, and is chief science officer of FIAS Inc. (a software company) and chief science officer for Gogoband Inc. (a software and bedwetting device maker).

Eric Dobremez has served as a consultant for Allergan plc.

Pawel Kroll has served as a study investigator for Allergan plc.

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Background

- Neurogenic detrusor overactivity (NDO) is characterized by involuntary detrusor contractions during the bladder filling phase
- NDO can lead to high bladder pressures that can result in damage to the upper urinary tract and kidneys, and may require augmentation cystoplasty
- Urinary incontinence due to NDO can also significantly affect quality of life
- OnabotulinumtoxinA (onabotA) 200U is an approved treatment for NDO in adults but is not currently approved for use in a pediatric population

Objective

- This study evaluated the efficacy and safety of onabotA detrusor injection in children with NDO not adequately managed with anticholinergic therapy

Study Design

- This was a multicenter, randomized, double-blind study
- Maximum duration 48 weeks

Enrollment

- Children aged ≥5 to ≤17 years
- UI due to NDO caused by spinal dysraphism, spinal cord injury, or transverse myelitis
- Clean intermittent catheterization use was mandatory

Treatment

- Patients received a single treatment of onabotA (50U, 100U, or 200U; not to exceed 6 U/kg) delivered as 20 injections of 0.5 mL excluding the trigone
- Patients could request retreatment after week 12, with the repeat treatment to be administered in the extension study
- Those completing the study could enter an extension study

NDO, neurogenic detrusor overactivity; onabotA, onabotulinumtoxinA; UI, urinary incontinence.

Assessments

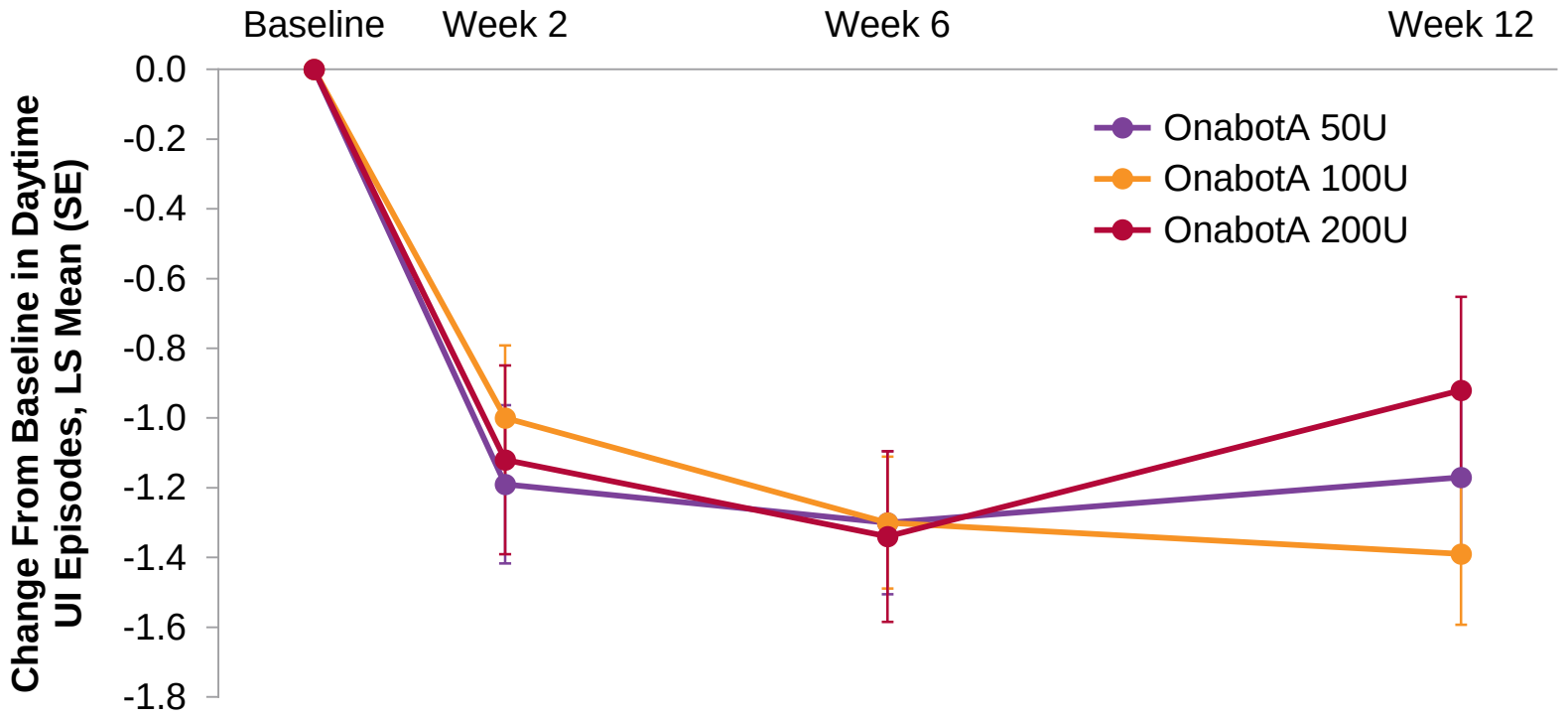
- **Primary endpoint**
  - Change from baseline in the daily average frequency of daytime urinary incontinence episodes. The primary timepoint was week 6
- **Secondary endpoints**
  - Change from baseline in average urine volume at first morning catheterization
  - Change from baseline in maximum detrusor pressure (cm H_2O) during the storage phase
- **Other endpoints**
  - Duration of effect (time to patient request and to qualification for retreatment)
  - Proportion of patients with a positive treatment response on the modified Treatment Benefit Scale ("greatly improved" or "improved")
- **Safety**
  - Adverse events

Baseline Demographics and Disease Characteristics

	OnabotA 50U (n=38)	OnabotA 100U (n=45)	OnabotA 200U (n=30)	Total (N=113)
Mean age (years)	11.4	10.8	11.9	11.3
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)
Average weight (SD) (kg)	41.9 (18.1)	40.1 (23.5)	46.9 (15.3)	42.5 (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	1 (3.3)	1 (0.9)

OnabotA, onabotulinumtoxinA; SD, standard deviation.

Change From Baseline in Daytime UI Episodes

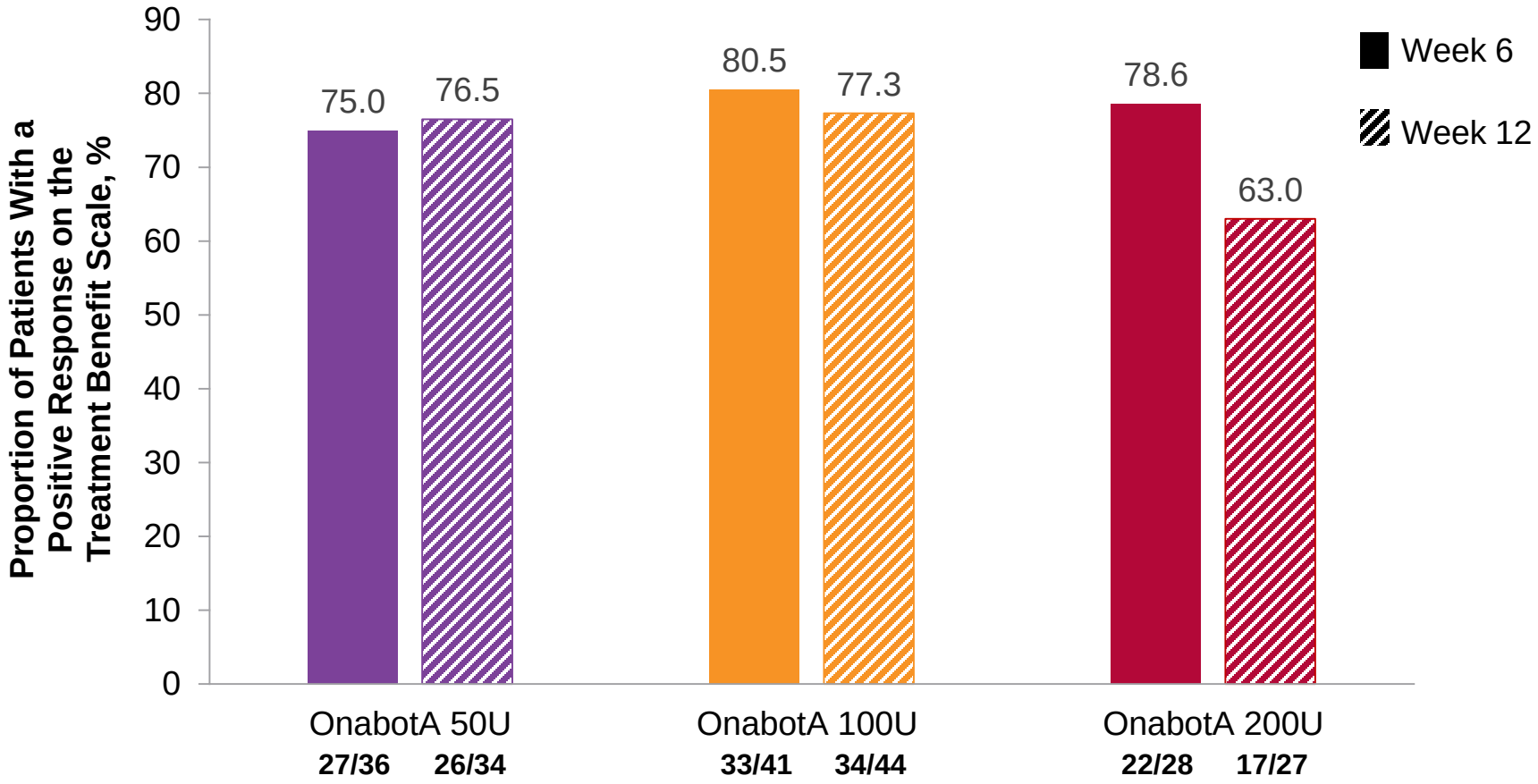


	OnabotA 50U (n=38)	OnabotA 100U (n=45)	OnabotA 200U (n=30)
Average baseline daytime UI episodes	2.81	2.99	3.68

All dose groups showed clinically meaningful reductions in UI of ≥1 episode/day

LS, least squares; onabotA, onabotulinumtoxinA; SE, standard error; UI, urinary incontinence.

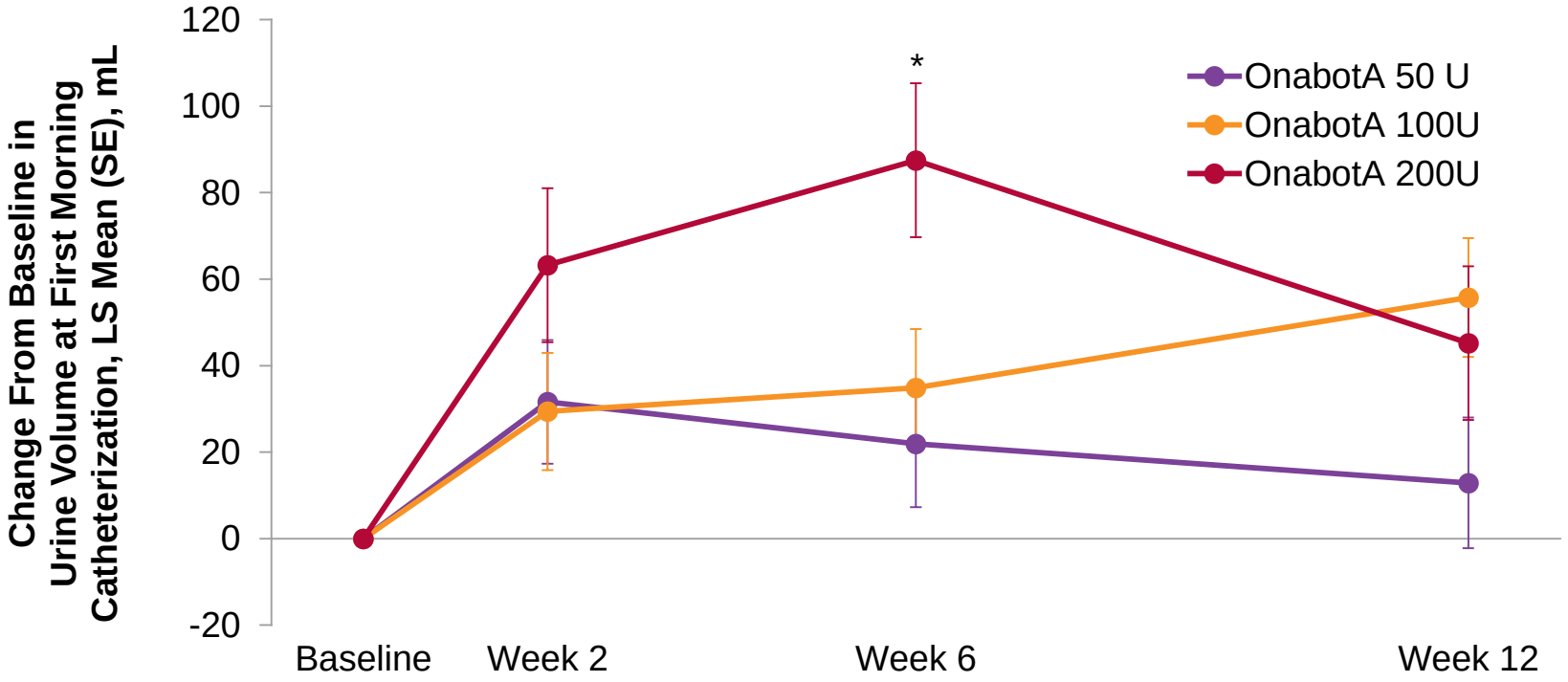
Proportion With a Positive Response (Improved/Greatly Improved) on Treatment Benefit Scale at 6 and 12 Weeks[a]



The majority of patients in all dose groups reported "great improvement" or "improvement"

[a]A positive response is defined as improvement or great improvement on the Treatment Benefit Scale (score of 1 or 2).
OnabotA, onabotulinumtoxinA.

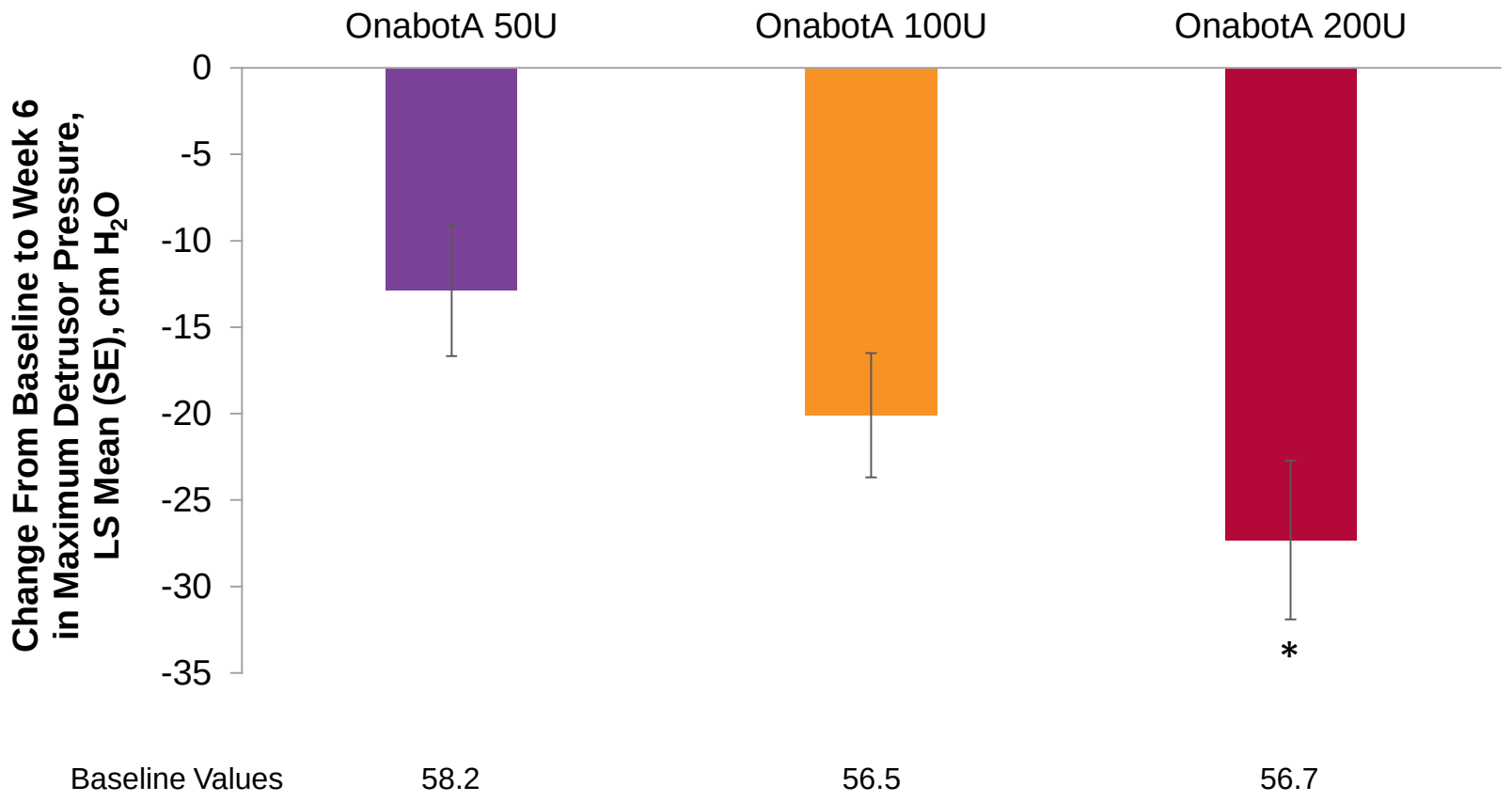
Change From Baseline in Urine Volume at First Morning Catheterization



	OnabotA 50U (n=38)	OnabotA 100U (n=45)	OnabotA 200U (n=30)
Average baseline urine volume at first catheterization, mL	203.46	164.19	187.69

*Significant vs 50U at week 6. *P*=.006. LS, least squares; onabot A, onabotulinumtoxinA; SE, standard error; UI, urinary incontinence.

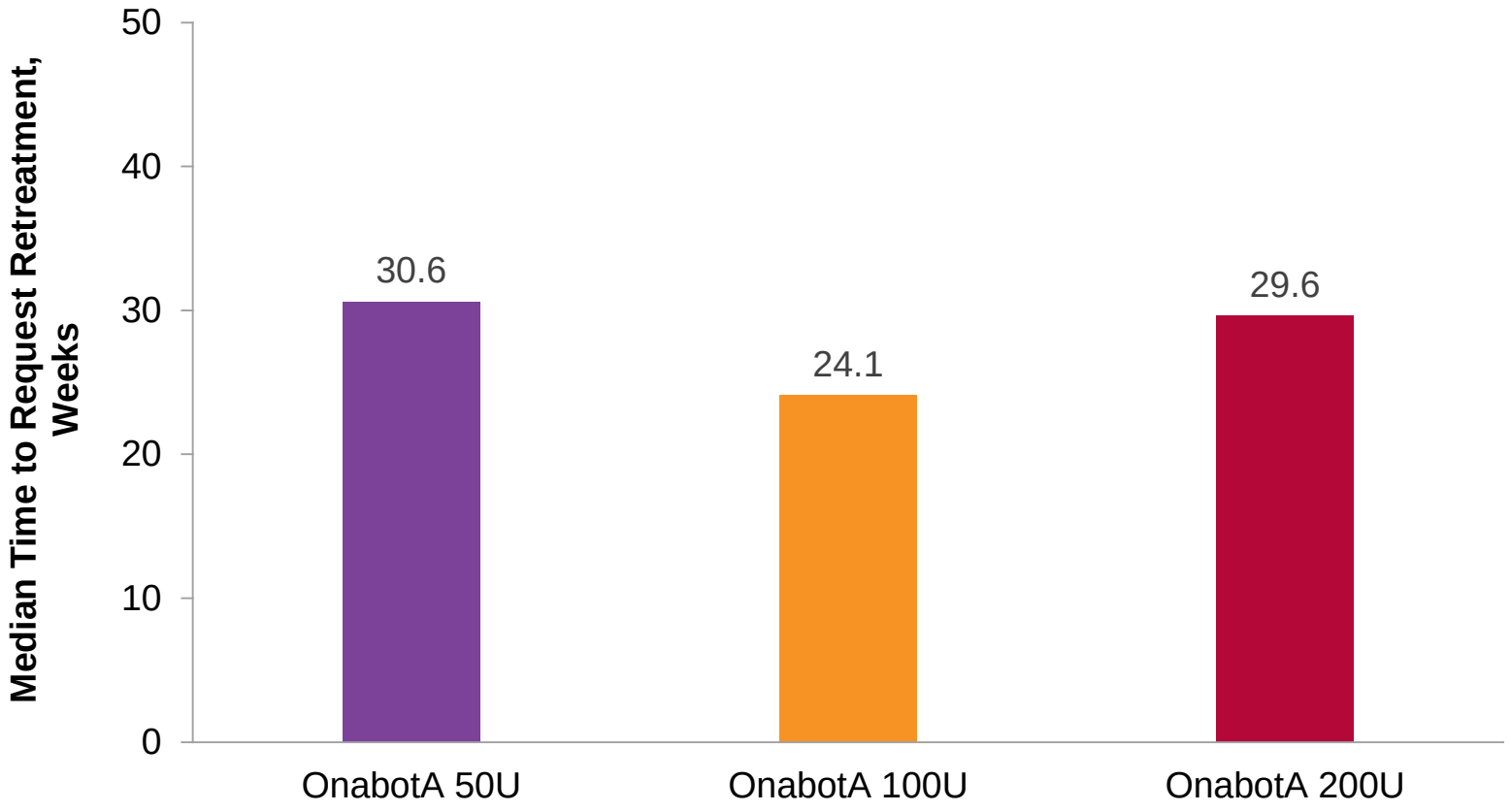
Change From Baseline to Week 6 in Maximum Detrusor Pressure During Storage



Dose response; 200U statistically significant vs 50U

*Significant vs 50U at week 6. *P*=.02. LS, least squares; onabotA, onabotulinumtoxinA; SE, standard error.

Duration of Effect: Request for Retreatment



Patients who received retreatment were retreated in the extension study
All patients completing the study were eligible to enter the open-label extension

OnabotA, onabotulinumtoxinA.

Most Common Adverse Events (≥3%) Over 12 Weeks[a]

n (%)	OnabotA 50U (n=38)	OnabotA 100U (n=45)	OnabotA 200U (n=30)	Total (N=113)
Any adverse event	18 (47.4)	30 (66.7)	18 (60.0)	66 (58.4)
Urinary tract infection[b]	7 (18.4)	13 (28.9)	2 (6.7)	22 (19.5)
Bacteriuria	5 (13.2)	5 (11.1)	6 (20.0)	16 (14.2)
Headache	1 (2.6)	4 (8.9)	1 (3.3)	6 (5.3)
Gastroenteritis	2 (5.3)	3 (6.7)	0 (0.0)	5 (4.4)
Leukocyturia	1 (2.6)	2 (4.4)	2 (6.7)	5 (4.4)
Pharyngitis	2 (5.3)	2 (4.4)	0 (0.0)	4 (3.5)
Nasopharyngitis	0 (0.0)	1 (2.2)	3 (10.0)	4 (3.5)
Diarrhea	0 (0.0)	3 (6.7)	1 (3.3)	4 (3.5)
Abdominal pain	2 (5.3)	1 (2.2)	1 (3.3)	4 (3.5)

[a]≥3% in the total population. [b]Urinary tract infection (UTI) was defined as symptomatic UTI that, in the opinion of the investigator, required treatment. If urinalysis/culture results were reported that were considered clinically significant but did not fulfill this definition of a UTI, the findings were recorded as adverse events such as bacteriuria and leukocyturia. OnabotA, onabotulinumtoxinA.

Annualized Rates of Urinary Tract Infection[a]

	6 Months Prior to Study Entry			Full Treatment Period		
	OnabotA 50U	OnabotA 100U	OnabotA 200U	OnabotA 50U	OnabotA 100U	OnabotA 200U
n/N (%)	7/38 (18.4)	10/45 (22.2)	7/30 (23.3)	11/38 (28.9)	15/45 (33.3)	7/30 (23.3)
Total number of events	9	22	14	14	24	9
Total patient-years	19.0	22.5	15.0	21.0	23.8	15.9
Event rate per patient-year	0.47	0.98	0.93	0.67	1.01	0.57

Annualized UTI rates during the full treatment period were similar to the annualized UTI rates experienced by the same patients during the 6 months prior to study entry

[a]Urinary tract infection (UTI) was defined as symptomatic UTI that, in the opinion of the investigator, required treatment. If urinalysis/culture results were reported that were considered clinically significant but did not fulfill this definition of a UTI, the findings were recorded as adverse events such as bacteriuria and leukocyturia. OnabotA, onabotulinumtoxinA.

Efficacy

- **All 3 doses of onabotA** demonstrated clinical efficacy for treatment of **daytime UI** in children with NDO not adequately managed with anticholinergic therapy
- OnabotA **200U** showed clinically and statistically greater improvements **vs 50U** in measures of **maximum detrusor pressure** during storage and **volume at first morning catheterization**

Safety

- The safety profile was similar across the 3 doses, which were **well tolerated,** with **UTI** being the **most common** adverse event

NDO, neurogenic detrusor overactivity; OnabotA, onabotulinumtoxinA; UI, urinary incontinence; UTI, urinary tract infection.