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Incontinence

Efficacy and Safety of AbobotulinumtoxinA in Patients with Neurogenic Detrusor Overactivity Incontinence Performing Regular Clean Intermittent Catheterization: Pooled Results from Two Phase 3 Randomized Studies (CONTENT1 and CONTENT2)

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Abstract

Background: For patients with neurogenic detrusor overactivity incontinence (NDOI), treatment with oral medications is often unsatisfactory.
Objective: To assess the efficacy and safety of abobotulinumtoxinA (aboBoNT-A) for NDOI.
Design, setting, and participants: Two randomized, double-blind phase 3 studies (CONTENT1, NCT02660138; CONTENT2, NCT02660359) enrolled patients with NDOI who were regularly performing clean intermittent catheterization (CIC) and were inadequately managed with oral therapy. Pooled results from the first placebo-controlled treatment cycle are reported.
Intervention: Patients received injections of aboBoNT-A 600 U (n = 162) or 800 U (n = 161) or placebo (n = 162) into the detrusor muscle.
Outcome measurements and statistical analysis: The primary endpoint was the mean change from baseline in NDOI episodes per week at week 6. Secondary endpoints reported are the proportion of patients with no NDOI episodes, the volume per void, urodynamic parameters, and quality of life (QoL). Safety was also assessed. Statistical analyses were conducted for the pooled study populations (each aboBoNT-A dose vs placebo).

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Results and limitations: At week 6, NDOI episodes per week were significantly reduced in each aboBoNT-A group versus placebo (both $p < 0.001$) and the volume per void had significantly increased. Approximately one-third of patients in each aboBoNT-A dose group reported no NDOI episodes versus 3% of patients in the placebo group. Reductions in urinary incontinence (UI) were reflected in significantly greater improvements in UI-related QoL in the aboBoNT-A groups versus placebo. Urodynamic parameters (bladder capacity and detrusor pressure) were significantly improved with each aboBoNT-A dose versus placebo. Each aboBoNT-A dose was well tolerated. Symptomatic urinary tract infection was the most frequent treatment-emergent adverse event, with incidence comparable across the aboBoNT-A and placebo groups. The studies were terminated prematurely owing to slow recruitment and were not designed for statistical comparison between the two aboBoNT-A doses.

Conclusions: Intradetrusor aboBoNT-A is an effective treatment and alternative option for patients with NDOI who have an inadequate response to oral anticholinergics and are already performing CIC.

Patient summary: In patients with bladder muscle overactivity caused by neurological conditions (multiple sclerosis or spinal cord injury) and resulting in urinary incontinence, abobotulinumtoxinA injections improved their symptoms and bladder function, with no unexpected effects.

1. Introduction

Neurogenic detrusor overactivity incontinence (NDOI) is a chronic condition caused by lesions of the central nervous system that result in urinary incontinence (UI) [1]. NDOI frequently occurs in patients with multiple sclerosis (MS) or spinal cord injury (SCI) [2] and can cause substantial impairment of quality of life (QoL), social stigma, and embarrassment [3].

Patients with NDOI often have high detrusor filling pressures due to involuntary detrusor contractions (IDCs) during bladder storage, low bladder capacity, poor detrusor compliance (DC), and detrusor-sphincter dyssynergia [4]. Clean intermittent catheterization (CIC) is used to achieve regular, complete emptying of the bladder at low pressure [5,6], and is key in preventing residual urine in the bladder and high bladder pressure which can respectively lead to urinary tract infections (UTIs) and upper urinary tract damage requiring medical and/or surgical treatment [5–8].

OnabotulinumtoxinA (onaBoNT-A; BOTOX, Allergan) is a treatment approved for NDOI when anticholinergic therapy has failed [9–11]; however, CIC use was not required or standardized in clinical trials that supported its approval [12,13]. In patients not performing CIC, there was a dose-dependent increase in postvoid residual volume and de novo CIC use for urinary retention, and an increase in UTI incidence with onaBoNT-A versus placebo [12,13]. AbobotulinumtoxinA (aboBoNT-A; Dysport, Ipsen) has also shown efficacy for the management of NDOI [14–19], with a reduction in NDOI episodes, improvement in urodynamic parameters, and a possible dose effect observed [15,18,19].

Here we report pooled results from two phase 3 studies that assessed the safety and efficacy of aboBoNT-A in patients with NDOI routinely performing CIC. These represent the first large, prospective, placebo-controlled studies in this population.

2. Patients and methods

2.1. Study design and intervention

Two multicenter, randomized, parallel-group, phase 3 studies were conducted; each included a double-blind placebo-controlled (DBPC) cycle followed by double-blind repeated aboBoNT-A treatment cycles. CONTENT1 (NCT02660138) was conducted at 64 sites in North America, Europe, and Asia. CONTENT2 (NCT02660359) was conducted at 67 sites in the Americas, Oceania, Europe, and Asia.

In both studies, an independent person performed randomization in blocks on the basis of computer-generated randomization lists using an interactive response technology system, with stratification by NDOI etiology (SCI vs MS) and prior intradetrusor BoNT-A status (naïve vs non-naïve). Patients, investigators, and study staff were blinded to treatment assignment throughout the study; the appearance of the vials and their contents and the methods for reconstitution were identical. Patients were randomized 2:2:1:1 to receive aboBoNT-A 600 U or 800 U for all cycles, placebo in the DBPC cycle, and then either aboBoNT-A 600 U or 800 U on fulfillment of the retreatment criteria. This manuscript focuses on the DBPC cycle results only.

Patients remained in the DBPC cycle either until the retreatment criteria were fulfilled, until the study end at 104 wk after first treatment, or until withdrawal/premature discontinuation from the study. Patients could request retreatment ≥12 wk after treatment if they had a <30% reduction from baseline in weekly NDOI episodes and there were no safety concerns on retreatment assessment.

Study treatments were administered into the detrusor muscle via cystoscopy (30 injection sites; 0.5 ml per site), avoiding the trigone. Patients received prophylactic antibiotics (determined according to a recent urine culture and sensitivity test where possible) for ≥3 d before and 3 d after treatment administration.

2.2. Study population

Eligible patients were aged between 18 and 80 yr; had NDOI for ≥3 mo before screening due to SCI (T1 level or lower, occurring ≥6 mo before screening) or clinically stable MS (per investigator's opinion, with no

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exacerbations within ≥3 mo before screening); and had, on average, two or more NDOI episodes per day with two or fewer NDOI-free days per week, as recorded in a 7-d bladder electronic diary (eDiary) during screening. In CONTENT1, NDO was confirmed by the presence of IDCs in trial-specific urodynamic studies (UDS) in all patients; in CONTENT2, this was confirmed either with trial-specific UDS or UDS within the preceding 12 mo. Eligible patients had an inadequate response after ≥4 wk of oral medications for NDOI treatment; patients receiving oral medications (eg, anticholinergics) were to continue their regimen during the study. All patients regularly performed CIC for ≥4 wk before screening (every 4–6 waking hours or more frequently). Exclusion criteria included current conditions or significant urological and pelvic disease (other than NDOI); surgeries that may impact bladder function <6 mo before screening; uninvestigated hematuria; conditions preventing CIC use; and a current indwelling bladder catheter or one removed within 4 wk before screening. BoNT-A treatment <9 mo before screening for urological conditions, such as detrusor treatment (<3 mo for nonurological conditions), was not permitted.

2.3. Study assessments

Patients recorded the number of NDOI episodes per day they experienced over a 7-d period in an eDiary at baseline and at weeks 2, 6, and 12, and every 12 wk thereafter. The volume per void during a 24-h period was also recorded in the eDiary.

To assess disease-specific QoL, the 22-item Incontinence-QoL (I-QoL) questionnaire with a 5-point response scale (higher scores represent better QoL) [20] was completed by patients at baseline and weeks 6 and 12.

Trial-specific UDS were performed at baseline and week 6 for all patients in CONTENT1, and a subset of patients in CONTENT2. Patients undergoing UDS at week 6 received prophylactic antibiotics for ≥2 d starting on the day of the procedure. UDS were conducted according to International Continence Society recommendations [5]. Urodynamic parameters, including maximum cystometric capacity (MCC), maximum detrusor filling pressure (MDFP), volume at first IDC (V1stIDC), and DC, were measured via standard urodynamic filling cystometry and validated by independent central reviewers (Supplementary material).

Treatment-emergent adverse events (TEAEs) were monitored. Vital signs were assessed at screening, before and after treatment administration, and during follow-up. Blood and urine parameters were assessed at screening and during follow-up. A UTI was defined as a positive urine culture result with a bacterial count of $>10^5$ colony-forming units/ml, leukocyturia of >5 cells per high-power field, and/or symptoms suggestive of a UTI (symptoms may be atypical in the NDOI population).

2.4. Study endpoints

Endpoints were assessed for each dose of aboBoNT-A in comparison with placebo. The primary endpoint in each study was the change from baseline in weekly NDOI episodes at week 6.

Secondary endpoints included the response to treatment defined using different thresholds for the reduction in NDOI (including no NDOI episodes, 100% reduction); the change from baseline in volume per void (from spontaneous or CIC voids); the change from baseline in I-QoL total summary score and domain scores (avoidance and limiting behavior; psychosocial impact; and social embarrassment); response to treatment defined using an improvement in I-QoL total summary score of ≥11 points; the change from baseline in MCC, MDFP, V1stIDC, and DC; and response to treatment defined as no IDCs during storage at week 6.

2.5. Statistical analysis

As these two studies used the same design and showed similar baseline patient characteristics and efficacy results, data were pooled to improve the precision of treatment effect estimates for efficacy endpoints. Results of tests for heterogeneity between the two studies, and for individual study results, are presented in the Supplementary material.

Efficacy analyses were performed on the randomized population per allocated treatment (regardless of whether they received treatment); safety analyses were performed for all patients who received any treatment. urodynamic endpoint analyses were conducted on the urodynamic population comprising all randomized patients in CONTENT1, and the subset of randomized patients in CONTENT2 for whom trial-specific UDS were performed.

Changes from baseline in diary parameters and QoL endpoints were analyzed using a mixed model repeated measures (MMRM) approach. Logistic generalized linear mixed models (GLMMs) were used to analyze the proportion of patients reaching response thresholds. Both models included treatment, visit (weeks 2, 6, and 12; weeks 6 and 12 only for I-QoL), treatment × visit interaction, stratification variables, and baseline values as fixed covariates. Statistical testing between each aboBoNT-A dose and placebo was performed at each visit using the respective contrast of the fitted model (ie, six partial tests for every endpoint [21]). After 12 wk, retreatment was possible, so no testing was performed after this time point. No statistical comparisons were made between the doses; the CONTENT studies were not designed or powered for that objective. Only 7-d eDiaries containing data for ≥5 d were analyzed. No imputation of missing data was performed for the primary analysis. To assess the impact of missing data for the primary efficacy endpoint, a sensitivity analysis was performed using multiple imputations (missing at random [MAR] assumption); a tipping point analysis was performed to examine the robustness of the result to departures from the MAR assumption. The change from baseline in urodynamic parameters was assessed with an analysis of covariance model. Analysis of patients with no IDCs at week 6 was based on a logistic regression model. Time to retreatment was analyzed using Kaplan-Meier survival analysis and a log-rank test; patients who were not retreated were censored at the last visit. In order to control the family-wise type 1 error, a hierarchical testing procedure was applied (Supplementary material). Safety data are summarized descriptively.

2.6. Ethics approval

Both studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice, the US Food and Drug Administration guidance for industry on computerized systems used in clinical trials, and local regulatory guidelines. All patients provided written informed consent.

3. Results

3.1. Patient disposition and baseline characteristics

The pooled population comprised 485 randomized patients (aboBoNT-A 600 U, *N* = 162; aboBoNT-A 800 U, *N* = 161; placebo, *N* = 162), of whom 483 received at least one study treatment between March 2016 and July 2019 in either CONTENT1 or CONTENT2 (Fig. 1). The pooled UDS population comprised 447 randomized patients (aboBoNT-A 600 U, *N* = 153; aboBoNT-A 800 U, *N* = 146; placebo, *N* = 148). The total number of randomized patients was lower than originally planned (330 patients per study), as both studies

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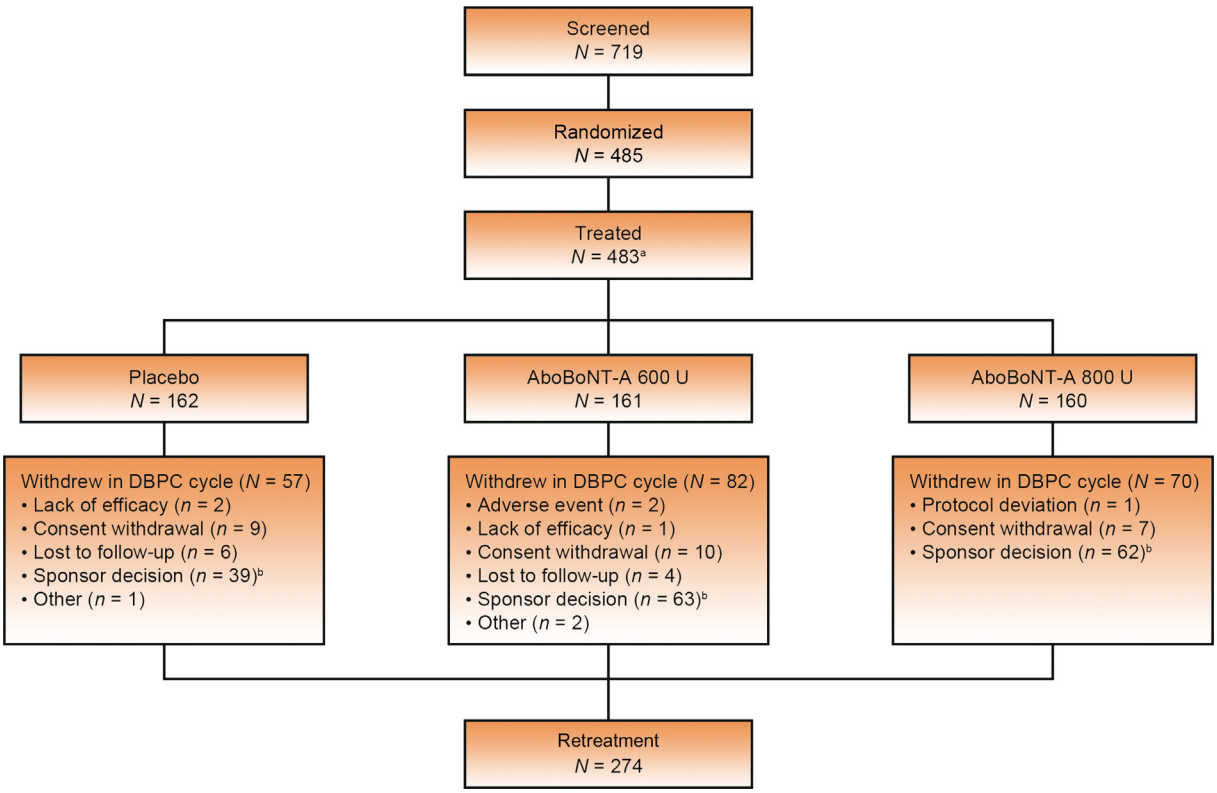

Fig. 1 – Disposition of patients (pooled population). [a] One patient randomized to aboBoNT-A 600 U and one to aboBoNT-A 800 U did not receive treatment and therefore did not enter the DBPC cycle. [b] Withdrawals for "sponsor decision" were a result of early termination of the study because of slow recruitment. Patients were discontinued at their next visit once 12 wk had elapsed from their last treatment. AboBoNT-A = abobotulinumtoxinA; DBPC = double-blind placebo-controlled.

were terminated prematurely in October 2018 owing to slow recruitment. Patients who were already randomized continued for ≥12 wk following their last treatment and then exited the study.

Baseline characteristics were generally well balanced between the treatment groups (Table 1). In the pooled population, 61% of patients were male, 70% had NDOI due to SCI and 30% due to MS, and 48% continued taking anticholinergics and/or β3 agonists at baseline. Patients had impaired bladder function in terms of both bladder ability to effectively store urine (as evidenced by both low MCC and V1stIDC) and elevated bladder filling pressure (high MDFP; Table 1). UTIs were commonly reported as occurring before study treatment (36% at any time, 19% in the last 6 mo) and 29% of patients had received previous intradetrusor BoNT-A treatment.

Patient disposition and baseline characteristics for the individual studies are shown in Supplementary Figure 1 and Supplementary Table 1.

3.2. *Efficacy*

Pooled results for eDiary parameters, QoL, and urodynamic parameters are presented in Table 2. Results for individual studies are presented in Supplementary Table 2.

3.2.1. *Reduction in NDOI episodes and total volume per void (spontaneous or CIC voids)*

At baseline, patients reported a similar number of weekly NDOI episodes across the treatment groups (Table 1). At weeks 2, 6 (primary endpoint), and 12, significantly greater reductions from baseline in weekly NDOI episodes were achieved with aboBoNT-A 600 U and 800 U versus placebo (all $p < 0.001$; Fig. 2A). Reductions were similar in both aboBoNT-A groups, with a least-squares mean reduction in NDOI episodes at week 6 of −22.7 and −23.6, respectively (Table 2 and Fig. 2A). At week 6, a significantly higher proportion of patients in each aboBoNT-A group versus placebo achieved a reduction in weekly NDOI episodes of ≥50%, ≥75%, or 100% (ie, no NDOI episodes, dry for the full week; all $p < 0.001$; Table 2). Approximately one-third of patients in each aboBoNT-A group reported no NDOI episodes, compared with 3% of patients in the placebo group.

Significant improvements in total volume per void (from spontaneous or CIC voids per eDiary data) were observed with each aboBoNT-A dose, with a minimal difference between doses, at weeks 2, 6, and 12 (all $p < 0.001$; Fig. 2B). Results for sensitivity analyses were consistent with the main analysis (Supplementary material).

3.2.2. *Disease-specific QoL outcomes*

Significantly greater improvements in I-QoL total summary scores and domain scores were observed in each aboBoNT-A group versus placebo from baseline to week 6 (both groups $p < 0.001$; Fig. 3A and Table 2). More than 60% of patients in both aboBoNT-A groups achieved improvement in I-QoL total summary score of ≥11 points at week 6 (both groups $p < 0.001$) versus 32% in the placebo group (Fig. 3B). Similar results were observed for each individual domain (Table 2).

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Table 1 – Baseline characteristics

Parameter	Placebo	AboBoNT-A 600 U	AboBoNT-A 800 U
Pooled randomized population, *N*	162	162	161
Median age, yr (IQR)	43.0 (21.0)	42.0 (18.0)	42.0 (23.0)
Age >65 yr, *n* (%)	12 (7)	8 (5)	16 (10)
Male, *n* (%)	88 (54)	106 (65)	101 (63)
Non-naïve BoNT-A status, *n* (%)	43 (27)	46 (28)	50 (31)
NDOI etiology, *n* (%)			
Spinal cord injury	113 (70)	114 (70)	114 (71)
Multiple sclerosis	49 (30)	48 (30)	47 (29)
Median duration of NDOI symptoms, mo (IQR)			
Spinal cord injury	76.0 (142.0)	79.5 (118.0)	60.5 (110.0)
Multiple sclerosis	83.0 (105.0)	94.0 (109.0)	102.5 (142.0)
Current anticholinergic and/or β3 agonist use, *n* (%)	72 (44)	77 (48)	84 (52)
Median daily CIC frequency at screening (IQR)	4.7 (1.8)	5.0 (2.2)	4.9 (2.0)
Patients with data, *n*	156	156	157
Prior UTI within 6 mo of screening, *n* (%)	25 (15)	28 (17)	38 (24)
Median NDOI episodes per week (IQR)	28.0 (18.3)	26.0 (20.5)	29.0 (18.0)
Patients with data, *n*	156	156	157
Median total volume per void, ml (IQR)	219.3 (146.2)	217.1 (141.7)	224.1 (124.7)
Patients with data, *n*	155	156	156
Median I-QoL total summary score (IQR)	36.9 (31.8)	33.0 (31.8)	30.7 (30.7)
Patients with data, *n*	162	157	161
Urodynamics population, *N*	148	153	146
Median maximum cystometric capacity, ml (IQR)	198.0 (188.0)	216.5 (187.5)	249.0 (211.0)
Patients with data, *n*	147	152	145
Median MDFP, cm H_2O (IQR)	52.5 (43.0)	50.0 (35.0)	53.0 (41.0)
Patients with data, *n*	138	146	137
Median volume at first IDC, ml (IQR)	137.0 (150.5)	147.0 (136.0)	177.0 (180.0)
Patients with data, *n*	140	143	135
Median detrusor compliance, ml/cm H_2O (IQR)	28.0 (34.0)	21.0 (27.0)	23.0 (33.0)
Patients with data, *n*	137	147	137

AboBoNT-A = abobotulinumtoxinA; BoNT-A = botulinum toxin type A; CIC = clean intermittent catheterization; IDC = involuntary detrusor contraction; I-QoL = 22-item Incontinence-Quality of Life questionnaire; IQR = interquartile range; MDFP = maximum detrusor filling pressure; NDOI = neurogenic detrusor overactivity incontinence; UTI = urinary tract infection.

3.2.3. *Urodynamics*

A significant improvement in all urodynamic parameters was observed with both doses of aboBoNT-A versus placebo, with numerically greater responses with aboBoNT-A 800 U than with 600 U for all parameters assessed except for DC.

Changes from baseline to week 6 in MCC and V1stIDC were significantly greater with each aboBoNT-A dose versus placebo (both doses $p < 0.001$; Table 2). The proportions of patients with no IDCs during storage were significantly higher and the reductions from baseline in MDFP were significantly greater in each aboBoNT-A group versus placebo at week 6 (both doses $p < 0.001$; Fig. 3C,D). Similarly, the change from baseline in DC was significantly greater with each aboBoNT-A dose versus placebo (both doses $p < 0.01$; Table 2).

3.2.4. *Time to retreatment*

The median time from first study treatment to retreatment was longer in the aboBoNT-A 600 U group (47 wk, 95% confidence interval [CI] 36–61) and aboBoNT-A 800 U group (39 wk, 95% CI 34–46) than in the placebo group (22 wk, 95% CI 18–25). Regardless of aboBoNT-A dose, >40% of patients did not receive retreatment until after 48 wk from their initial aboBoNT-A treatment.

3.3. *Safety*

An overview of TEAEs during the DBPC cycle for the pooled population is shown in Table 3; individual study results are presented in Supplementary Table 3.

Overall, injections of aboBoNT-A were well tolerated. Two patients discontinued treatment because of a TEAE in the DBPC cycle: general physical health deterioration and cerebrovascular accident (both aboBoNT-A 600 U). Neither of these events was considered treatment-related, with the latter leading to the only death reported in the program (day 58).

The proportion of patients reporting TEAEs was generally comparable across the groups up to week 12, and slightly higher in the aboBoNT-A groups versus placebo across the full DBPC cycle, which was longer for aboBoNT-A (Table 3). There were no treatment-related serious TEAEs in any group.

Symptomatic UTI was the most frequent TEAE in all groups up to week 12 after injection and across the full DBPC cycle, with similar proportions in the aboBoNT-A 600 U and 800 U groups versus placebo (up to 12 wk after injection: 14% and 15% vs 17%; across the full DBPC cycle: 21% and 27% vs 20%, respectively). The incidence of serious UTIs was similar with placebo and aboBoNT-A 600 U, and slightly superior with aboBoNT-A 800 U. Acute pyelonephritis (not serious) occurred in two patients receiving aboBoNT-A 600 U and one patient receiving placebo across the full DBPC cycle. Serious UTIs occurred in <3% of patients across the full DBPC cycle (Table 3).

One patient with SCI who received aboBoNT-A 600 U reported autonomic dysreflexia during the first 12 wk after treatment that was not considered to be related to treatment.

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Table 2 – Model-based estimates of efficacy at week 6 (double-blind placebo-controlled cycle; pooled randomized population)

Efficacy outcome	Placebo	AboBoNT-A 600 U	AboBoNT-A 800 U
Pooled randomized population, *N*	162	162	161
Change in weekly NDO episodes from baseline [a]			
Least squares mean, *n* [SE]	−12.7 [1.3] (140)	−22.7 [1.3] (144)	−23.6 [1.3] (139)
Difference vs placebo (95% CI)		−10.0 (−13.5 to −6.5) ***	−10.9 (−14.4 to −7.4) ***
Threshold of improvement in weekly NDO episodes from baseline [b]			
≥50% reduction, *n*/*N* (%)	48/140 (34)	106/144 (74)	94/139 (68)
Odds ratio (95% CI) vs placebo		5.5 (3.3–9.2) ***	4.4 (2.7–7.3) ***
≥75% reduction, *n*/*N* (%)	21/140 (15)	90/144 (63)	80/139 (58)
Odds ratio (95% CI) vs placebo		9.3 (5.2–16.4) ***	8.3 (4.7–14.7) ***
100% reduction in UI, *n*/*N* (%)	4/140 (3)	52/144 (36)	40/139 (29)
Odds ratio (95% CI) vs placebo		18.9 (6.9–51.9)***	15.5 (5.6–42.9)***
Change in total volume per void from baseline (ml) [a]			
Least squares mean, *n* [SE]	−5.9 [11.2] (136)	85.1 [11.1] (138)	98.1 [11.1] (136)
Difference vs placebo (95% CI) [a]		91.0 (61.4–120.5) ***	104.0 (74.4–133.5) ***
Change in I-QoL total summary score from baseline [a]			
Least squares mean, *n* [SE]	7.1 [1.8] (149)	22.1 [1.8] (147)	22.2 [1.7] (150)
Difference vs placebo (95% CI)		15.0 (10.4–19.6) ***	15.1 (10.5–19.7) ***
Change in I-QoL domain scores from baseline [a]			
Avoidance and limiting behavior			
Least squares mean, *n* [SE]	7.1 [1.8] (149)	22.0 [1.8] (147)	22.9 [1.8] (150)
Difference vs placebo (95% CI)		14.9 (10.2–19.5) ***	15.8 (11.2–20.4) ***
Psychological impact			
Least squares mean, *n* [SE]	7.4 [1.9] (149)	21.3 [1.9] (147)	20.8 [1.8] (150)
Difference vs placebo (95% CI)		13.9 (8.9–18.8) ***	13.4 (8.4–18.3) ***
Social embarrassment			
Least squares mean, *n* [SE]	6.7 [2.0] (149)	23.5 [2.0] (147)	23.2 [2.0] (150)
Difference vs placebo (95% CI)		16.8 (11.5–22.1) ***	16.5 (11.2–21.8) ***
Increase in I-QoL total summary score from baseline of ≥11 points [b]			
Patients, *n*/*N* (%)	47/149 (32)	95/147 (65)	94/150 (63)
Odds ratio (95% CI) vs placebo		3.9 (2.4–6.5) ***	3.5 (2.1–5.7) ***
Urodynamic population (*N*)	148	153	146
Change in maximum cystometric capacity from baseline (ml) [c]			
Least squares mean, *n* [SE]	−4.0 [13.9] (128)	164.6 [13.6] (136)	175.8 [13.7] (133)
Difference vs placebo (95% CI)		168.5 (132.4–204.7) ***	179.8 (143.5–216.1) ***
Change in maximum detrusor filling pressure from baseline (cm H_2O) [c]			
Least squares mean, *n* [SE]	−4.9 [2.3] (112)	−33.1 [2.2] (125)	−35.4 [2.2] (122)
Difference vs placebo (95% CI)		−28.2 (−34.0 to −22.3) ***	−30.4 (−36.3 to −24.5) ***
Change in volume at first IDC from baseline (ml) [c]			
Least squares mean, *n* [SE]	12.3 [14.7] (123)	166.4 [14.4] (128)	191.2 [14.6] (124)
Difference vs placebo (95% CI)		154.1 (116.0–192.1) ***	178.9 (140.4–217.5) ***
Change in detrusor compliance from baseline (ml/cm H_2O) [c]			
Least squares mean, *n* [SE]	2.8 [7.0] (114)	29.3 [6.7] (126)	28.6 [6.7] (123)
Difference vs placebo (95% CI)		26.5 (8.6–44.4) **	25.8 (7.9–43.7) **
No IDC during storage [d]			
Patients, *n*/*N* (%)	8/122 (7)	59/134 (44)	71/129 (55)
Odds ratio (95% CI) vs placebo		11.9 (5.3–26.6) ***	18.6 (8.3–41.7) ***

aboBoNT-A' (x2)= abobotulinumtoxinA; BoNT-A = botulinum toxin type A; CI = confidence interval; IDC = involuntary detrusor contraction; I-QoL = 22-item Incontinence-Quality of Life questionnaire; NDOI = neurogenic detrusor overactivity incontinence; SE = standard error.

** $p < 0.01$; *** $p < 0.001$ versus placebo.

[a] According to a mixed model of repeated measures with treatment group, visits (weeks 2, 6, and 12 for weekly NDOI episodes and volume per void; weeks 6 and 12 for I-QoL), treatment × visit interaction, stratification factors (NDOI etiology [spinal cord injury or multiple sclerosis], prior intradetrusor BoNT [naïve or non-naïve]), study baseline value, and study as fixed effect variables, and patient as a random effect. Only the results for each AboBoNT-A dose versus placebo at week 6 are presented.

[b] According to a logistic generalized linear mixed model with treatment group, stratification factors (NDOI etiology, prior intradetrusor BoNT), visits (weeks 2, 6, and 12 for weekly NDOI episodes; weeks 6 and 12 for I-QoL), treatment × visit interaction, study baseline-× visit interaction, study, and study baseline as fixed effects, and patient as a random effect. Only the results for each AboBoNT-A dose versus placebo at week 6 are presented.

[c] According to an analysis of covariance model used with treatment group, stratification factors (NDOI etiology, prior intradetrusor BoNT), study baseline value, and study as fixed effect variables.

[d] According to a logistic regression model with treatment group, stratification factors (NDOI etiology, prior intradetrusor BoNT) and study as fixed variables.

No clinically meaningful changes attributable to aboBoNT-A were observed in hematology, biochemistry, urinalysis, or vital-sign parameters (data not shown).

4. Discussion

The CONTENT studies demonstrate that aboBoNT-A injections improve bladder symptoms, urodynamic parameters, and incontinence-related QoL in patients with NDOI regularly performing CIC, with statistically significant efficacy achieved by week 2 after injection in comparison to placebo.

Reductions in weekly NDOI episodes observed with aboBoNT-A 600 U or 800 U at week 6 in the present study are consistent with those reported in two pivotal phase 3 studies on onaBoNT-A [12,13].

Although all patients were performing regular CIC, patients experienced on average 30–40 NDOI episodes per

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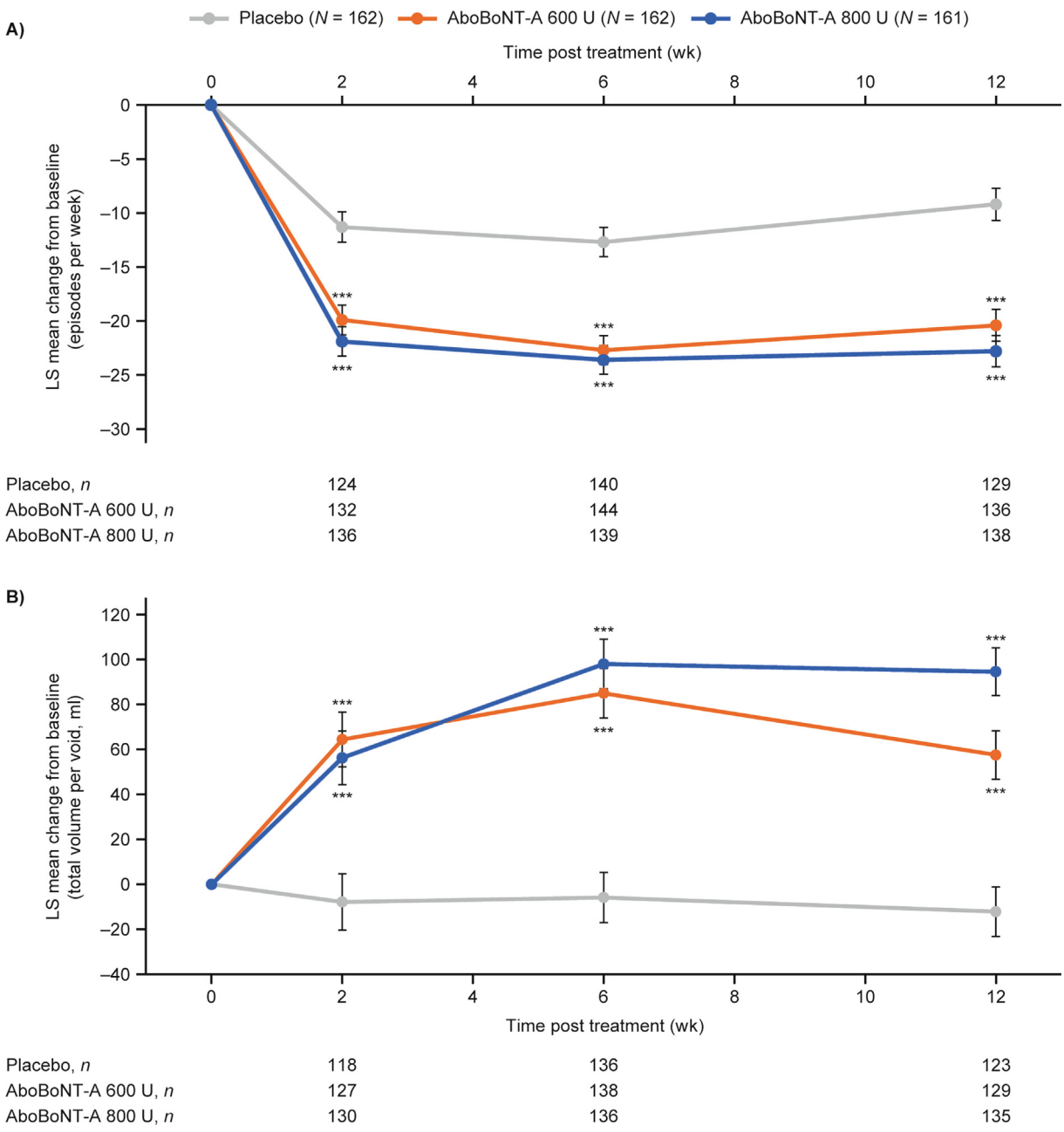

Fig. 2 – Change from baseline over the DBPC cycle in (A) weekly NDOI episodes and (B) total volume per void (spontaneous or clean intermittent catheterization voids) for the pooled randomized population. Mixed-model repeated measures was used to assess differences in the change from baseline between each aboBoNT-A group (600 U or 800 U) and placebo at each time point (weeks 2, 6, and 12), with treatment group, visits (weeks 2, 6, and 12), treatment × visit interaction, stratification factors (NDOI etiology [spinal cord injury or multiple sclerosis], prior intradetrusor BoNT [naïve or non-naïve]), and study baseline value as fixed effect variables, and patient as a random effect. Data are the least-squares mean ± standard error. *** $p < 0.001$ for aboBoNT-A (600 U or 800 U) versus placebo. AboBoNT-A = abobotulinumtoxinA; BoNT-A = botulinum toxin type A; DBPC = double-blind placebo-controlled; NDOI, neurogenic detrusor overactivity incontinence.

week at baseline. Following 6 wk of treatment, approximately 30% of patients treated with aboBoNT-A reported no NDOI episodes over a full week versus 3% of those receiving placebo. Despite differences in enrolled populations, the delta between the aboBoNT-A and placebo groups was similar to that reported in studies of onaBoNT-A in which 36–41% of patients receiving onaBoNT-A and 8–10% receiving placebo achieved 100% reduction in weekly NDOI episodes [12,13]. The ability of the bladder to store urine also improved following aboBoNT-A treatment, demonstrated by significant improvements in volume per void versus placebo. The CONTENT studies also demonstrated clinically relevant and significant improvements in disease-related QoL with aboBoNT-A versus placebo; a high proportion of patients achieved improvements that exceeded the established minimally important difference for the I-QoL total summary score (≥11 points) in patients with NDOI [22].

A long time to retreatment was observed in patients receiving aboBoNT-A in the pooled CONTENT studies (up to 47 wk). These data are not available for the pooled

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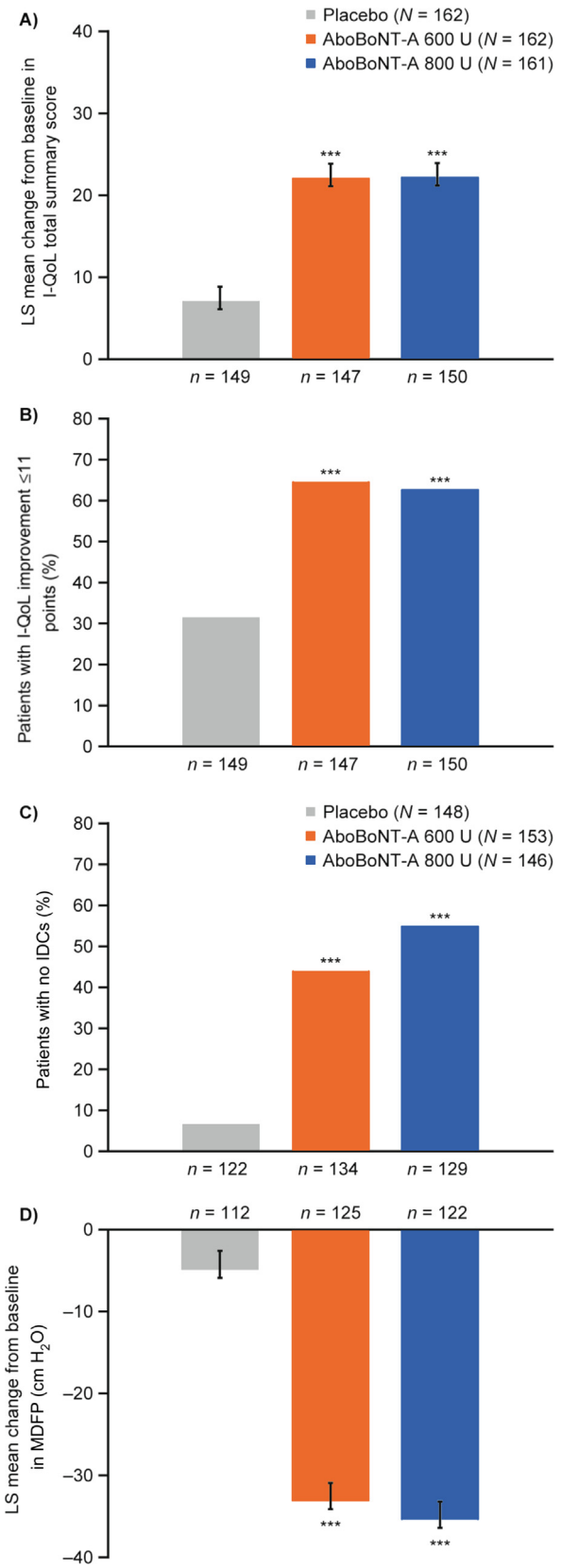

onaBoNT-A phase 3 studies; retreatment criteria differed between the studies. Nevertheless, the median time to retreatment in the onaBoNT-A study in which there was a comparable UI threshold for the retreatment criterion was 42 wk, consistent with what was observed in the CONTENT program [13]. No clear difference was observed between aboBoNT-A doses, perhaps owing to the large range for the estimate and premature study discontinuation. The time to retreatment may also have been influenced by logistic factors at individual centers that affected scheduling of retreatment assessment and administration. Patients also had to return to a level of UI relative to their baseline value to qualify for retreatment. Therefore, this duration may not reflect real-life clinical needs. Furthermore, had findings from UDS performed during the course of the trial been taken into account, some patients might have qualified earlier for retreatment.

Large improvements in bladder function and storage following aboBoNT-A treatment were also evidenced by UDS data, in line with previous studies on the treatment of NDOI with aboBoNT-A [14–19] or onaBoNT-A [12,13]. The significant reduction in MDFP suggests that aboBoNT-A treatment may reduce the risk of renal complications associated with long-term high bladder pressure, although longer-term data are needed [10]. While no formal statistical comparisons between the aboBoNT-A doses were performed in CONTENT1 or CONTENT2, mean improvements in urodynamic parameters were generally numerically greater with aboBoNT-A 800 U than with 600 U. These findings corroborate results for the reduction in frequency of UI episodes and increase in volume per void with each aboBoNT-A dose in comparison to placebo. However, in contrast to clinical symptoms, a minimal placebo

Fig. 3 – Incontinence-related QoL and urodynamic parameters at week 6 (DBPC cycle; pooled randomized population). (A) Change from baseline in I-QoL total summary score according to mixed-model repeated measures to assess the difference in change from baseline between each aboBoNT-A dose group (600 U or 800 U) and placebo at weeks 6 and 12, with treatment group, visits (weeks 6 and 12), treatment × visit interaction, stratification factors (NDOI etiology [spinal cord injury or multiple sclerosis], prior intradetrusor BoNT-A [naïve or non-naïve]), study baseline value, and study as fixed effect variables, and patient as a random effect. Data are the least square (LS) mean ± standard error (SE); week 6 data only are presented. (B) Proportion of patients experiencing an improvement in I-QoL total summary score of ≥11 points according to logistic GLMM to assess the difference between each aboBoNT-A dose group (600 U or 800 U) and placebo, with treatment group, stratification factors (NDOI etiology, prior intradetrusor BoNT-A), visit (weeks 6 and 12), treatment × visit interaction, study baseline × visit interaction, study, and study baseline as fixed effects, and patient as a random effect. Week 6 data only are presented. (C) Proportion of patients with no IDCs according to a logistic regression model to assess the difference between each aboBoNT-A group (600 U or 800 U) and placebo at week 6, with treatment group, stratification factors (NDOI etiology, prior intradetrusor BoNT-A), and study as fixed variables. (D) Change from baseline in MDFP according to an analysis of covariance model to assess the difference in change from baseline between each aboBoNT-A dose group (600 U or 800 U) and placebo at week 6, with treatment group, stratification factors (NDOI etiology, prior intradetrusor BoNT-A), study baseline value, and study as fixed effect variables. Data are the LS mean ± SE. *** $p < 0.001$ for aboBoNT-A (600 U or 800 U) versus placebo. AboBoNT-A = abobotulinumtoxinA; BoNT-A = botulinum toxin type A; DBPC = double-blind placebo-controlled; IDC = involuntary detrusor contraction; I-QoL = 22-item Incontinence-Quality of Life questionnaire; MDFP, maximum detrusor filling pressure; NDOI, neurogenic detrusor overactivity incontinence.

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Table 3 – Summary of TEAEs up to week 12 and over the full DBPC treatment cycle reported for ≥5% of patients in any treatment group (DBPC, pooled safety population)

Assessment period	Placebo	AboBoNT-A 600 U	AboBoNT-A 800 U
Pooled safety population, N	161	160	162
First 12 wk of DBPC cycle, *n* (%)			
Any TEAE	66 (41)	74 (46)	68 (42)
Any serious TEAE	4 (3)	9 (6)	6 (4)
TEAEs with incidence ≥5% in ≥1 aboBoNT-A group			
Urinary tract infection [a]	27 (17)	23 (14)	24 (15)
Full DBPC cycle, *n* (%)			
Any TEAE	78 (49)	88 (55)	88 (54)
Any serious TEAE	8 (5)	18 (11)	14 (9)
TEAEs with incidence ≥5% in ≥1 aboBoNT-A group			
Urinary tract infection [a]	32 (20)	33 (21)	44 (27)
Hematuria	5 (3)	9 (6)	6 (4)

AboBoNT-A = abobotulinumtoxinA; DBPC = double-blind placebo-controlled; TEAE = treatment-emergent adverse event.

[a] Urinary tract infection was defined as a positive urine culture result with a bacteria count of $>10^5$ colony-forming units/ml, leukocyturia of >5 cells per high-power field, and symptoms suggestive of a urinary tract infection (may be atypical symptoms in the population with neurogenic detrusor overactivity incontinence). If a patient experienced more than one event in a category, the patient is counted only once in that category.

effect was observed across urodynamic parameters, highlighting the relevance of performing UDS.

Both aboBoNT-A doses were well tolerated. The only adverse event occurring in more than 5% of patients was UTI in the first 12 wk. Notably, rates of symptomatic UTI were similar between the aboBoNT-A and placebo groups (14–15% vs 17% during the first 12 wk after treatment) and were comparable to the proportions of patients with a medical history of UTI in the 6 mo before first treatment (17–24% vs 15%). Rates of UTI in the onaBoNT-A studies (all UTIs and not just protocol-defined symptomatic UTIs according to the CONTENT program) were also similar across treatment groups for the subgroup of patients with SCI, the majority of whom were performing CIC [12,13].

5. Limitations

The number of randomized patients was more limited than planned in both studies, and not all patients in CONTENT2 underwent postinjection UDS, although the large majority did (85%). The amount of missing data was quite high and assumed MAR, therefore their impact on results cannot be ruled out [23]; however, results from all sensitivity analyses are consistent with those from the main analyses. These studies were not designed or powered to compare efficacy between the two aboBoNT-A doses. Only patients regularly performing CIC were enrolled and therefore the results may not be applicable to patients not performing CIC. Longer follow-up for patients treated with aboBoNT-A would be required to fully evaluate long-term efficacy over repeated treatments and to determine if treatment discontinuation and failure rates over time mimic those reported for onaBoNT-A [24,25].

6. Conclusions

In patients with NDOI who were regularly performing CIC, treatment with intradetrusor aboBoNT-A 600 U and 800 U resulted in clinically relevant and highly statistically significant improvements in NDOI and bladder storage symptoms and multiple urodynamic parameters in comparison to placebo. aboBoNT-A injections were well tolerated, with no clinically relevant difference in UTI incidence in comparison to placebo and an improvement in disease-related QoL. Intradetrusor aboBoNT-A can be considered an effective treatment and alternative option for patients with NDOI performing CIC who have an inadequate response to oral anticholinergics.

Author contributions: Michael Kennelly had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kennelly, Herschorn, Onem, Thompson, Volteau, Denys, Cruz.
Acquisition of data: Abrams, Onem, Giannantoni.
Analysis and interpretation of data: Kennelly, Herschorn, Thompson, Vilain, Denys, Cruz.
Drafting of the manuscript: Kennelly, Abrams, Onem, Thompson, Vilain, Volteau, Denys, Giannantoni.
Critical revision of the manuscript for important intellectual content: Kennelly, Herschorn, Abrams, Onem, del Rosario Figueroa Coz, Thompson, Vilain, Volteau, Denys, Giannantoni, Kibanov Solomonov, Cruz, Manu-Marin.
Statistical analysis: Volteau.
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Other (*patient enrolment and evaluation*): del Rosario Figueroa Coz, Kibanov Solomonov, Giannantoni.

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***Data sharing statement*:** Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 mo and ending 5 yr after publication; after this time, only raw data may be available.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2022.03.010.

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