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Efficacy and safety of onabotulinumtoxinA for the treatment of overactive bladder in men and women: A pooled analysis

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Abstract

Background: This pooled analysis of randomized controlled studies investigated the safety and efficacy of onabotulinumtoxinA in male and female patients with overactive bladder (OAB).

Methods: Data were pooled from four similarly designed trials in North America and Europe. Adults with idiopathic OAB for ≥6 months inadequately managed by at least one anticholinergic were randomized 1:1 or 2:1 to receive onabotulinumtoxinA 100 U or matched placebo in Cycle 1 and could request open-label retreatment with onabotulinumtoxinA 100 U at ≥12 weeks. Efficacy outcomes at Week 12 included the primary endpoint of mean urinary incontinence (UI) episodes per day and other variables, such as the proportion of patients with ≥50% reduction in daily UI episodes. Safety was assessed by monitoring treatment-emergent adverse events (TEAEs). Analyses by sex were descriptive. Males were further analyzed by benign prostatic hyperplasia (BPH) diagnosis status.

Results: In the pooled population ($N = 1564$), there were 194 males (12.4%) and 1370 females (87.6%). Mean number of baseline UI episodes per day was 4.9 in males and 5.5 in females. At Week 12, numerically greater mean reductions from baseline in number of daily UI episodes were observed with the onabotulinumtoxinA 100 U group (females: −3.0; males: −2.2) versus placebo (females: −1.1; males: −1.3). Achievement of ≥50% reduction in daily UI episodes was numerically greater with onabotulinumtoxinA 100 U (females: 64.8%; males: 61.2%) versus placebo (females: 30.6%; males: 44.8%), and numerically higher in males without BPH (onabotulinumtoxinA: 65.1%; placebo: 50.9%) versus with BPH (onabotulinumtoxinA: 54.3%; placebo: 36.6%). A total of 34.7% of males and 39.4% of females experienced at least one TEAE in the first 12 weeks during treatment Cycle 1. Urinary tract infection

rate was 13.1% in females and 4.2% in males; incidence of hematuria was 6.8% in males and 1.1% in females. Incidence of urinary retention (defined as incomplete emptying, requiring catheterization) was 2.7% in females and 4.7% in males.

Conclusion: OnabotulinumtoxinA 100 U was efficacious and well tolerated in men and women with OAB, including in males with and without BPH. No new safety findings were identified when data were analyzed by sex.

KEYWORDS

benign prostatic hyperplasia, botulinum toxin type A, male, overactive bladder, urinary incontinence

1 | INTRODUCTION

Overactive bladder (OAB) is a common urinary condition with a reported prevalence of 15.6%–27.2% in men and 16.9%–43.1% in women.[1–4] Common OAB symptoms, including urinary urgency, increased frequency of urination, and nocturia, are more frequently reported with increasing age.[5] OAB is often accompanied by urinary incontinence (UI), which can have profound effects on quality of life.[6,7] In the multinational, population-based EpiLUTS study, OAB occurring with urgency and/or UI was reportedly more prevalent in women (35.6%–39.8%), but it is not uncommon in men (23.4%–25.2%).[1] A subsequent multinational, population-based EPIC study also found high rates of OAB with UI in both women and men.[2]

Although OAB is prevalent in both men and women, male patients are often underrepresented in OAB studies, and OAB may be underdiagnosed and undertreated in males.[8–10] It can be challenging to diagnose OAB in men with benign prostatic hyperplasia (BPH), as there may be some overlap of urinary symptoms between the two conditions; however, OAB also includes symptoms that are distinct from BPH.[8,11] In BPH, voiding problems, such as urinary hesitancy and weak/intermittent urine stream,[6,8] may result from an obstruction of the bladder outlet due to prostatic enlargement.[12] On the other hand, OAB symptoms reflect storage dysfunction, such as frequent urination or urgency with or without UI, resulting from detrusor overactivity.[6,8,12] Despite these differences, a retrospective study found that many male patients with OAB symptoms received treatment for BPH despite not having a BPH diagnosis, suggesting the possibility that some male patients with OAB may not be receiving proper diagnosis and treatment.[8]

Currently, there are no sex-specific treatment recommendations for OAB in the American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) guidelines.[13] Patients with OAB may benefit from noninvasive treatments such as behavioral therapies and incontinence management strategies. Patients may require treatment with pharmacotherapy, which includes oral medications such as anticholinergics or beta-3 agonists.[13] However, some patients experience lack of tolerability or inadequate response to oral medications or may have contraindications due to comorbidities.[14,15]

AUA/SUFU and European Association of Urology guidelines recommend minimally invasive treatment options, including onabotulinumtoxinA treatment, for appropriate patients with OAB who have an inadequate response or intolerance to pharmacotherapy or behavioral therapies.[13,15,16] It is also noted in the AUA guidelines that clinicians may offer patients with OAB and BPH these same treatment options.[13] OnabotulinumtoxinA has demonstrated efficacy and safety for the treatment of patients with OAB with UI in randomized, placebo-controlled Phase 3 studies.[17–20] Although these studies did not exclude male patients, they did not recruit them in large numbers. This pooled analysis investigated the safety and efficacy of onabotulinumtoxinA in subgroups of male and female patients with OAB. To enable a more robust assessment of efficacy in male patients and sex-specific safety considerations, data were pooled from four randomized controlled studies of onabotulinumtoxinA. Because an enlarged prostate can contribute to difficulty voiding,[12] data from male patients were further grouped by presence or absence of BPH.

2 | METHODS

2.1 | Study design

This study pooled efficacy and safety data from four similarly designed randomized, double-blind, placebo-controlled clinical trials conducted in North America and

Europe (Table S1): 191622-095 (NCT00910845),[17] 191622-520 (NCT00910520),[18] 191622-125 (NCT01767519),[19] and GMA-OAB-113 (NCT01945489).[20] Patients were randomized 1:1 or 2:1 (in study 125) to receive onabotulinumtoxinA 100 U or matched placebo in treatment Cycle 1 and could request retreatment in the open-label phase with onabotulinumtoxinA 100 U any time after 12 weeks posttreatment for symptom control. To qualify for retreatment, patients had to have at least two urgency urinary incontinence (UUI) episodes and no more than one UUI-free day during a 3-day period and postvoid residual (PVR) volume <200 mL. On the day of retreatment, patients had a negative urine dipstick reagent strip test and were asymptomatic for urinary tract infection (UTI), had discontinued antiplatelet/anticoagulant therapy (≥3 days), had a negative urine or serum pregnancy test for women of childbearing potential, had initiated appropriate antibiotic medication, and had no bladder stones since study entry. Patients received prophylactic antibiotics 1–3 days before treatment, on treatment day, and at least 1–3 days after treatment.

The long-term safety profile of onabotulinumtoxinA in males and females was further analyzed by pooling patients who received up to two treatments in studies 191622-095, 191622-520, 191622-125, and GMA-OAB-113, as well as patients from studies 191622-095 and 191622-520 who rolled over into the long-term extension study 191622-096 and were followed for up to 3 years. The studies complied with Good Clinical Practice regulations, study protocols were approved by the institutional review board and/or independent ethics committee at each study site, and all patients provided written informed consent before study commencement.

2.2 | Eligibility criteria

Eligible patients were adults with idiopathic OAB for ≥6 months who were inadequately managed by at least one anticholinergic agent (i.e., still incontinent despite ≥4 weeks of treatment or limiting side effects after ≥2 weeks). Patients included in the study had at least three urgency UI episodes recorded in the 3-day bladder diary, had at least eight micturitions per day, had a negative urine dipstick reagent strip test and were asymptomatic for UTI, and were willing and able to use clean intermittent catheterization (CIC) if needed. Patients were excluded from the study if they had OAB symptoms caused by a neurologic disease and evidence of urethral and/or bladder outlet obstruction (in the opinion of the investigator) at screening or randomization/Day 1. BPH was recorded as a clinical diagnosis per investigator's clinical judgment on the medical history case report form, but BPH alone was not exclusionary. Other exclusion criteria included at least two UTIs within 6 months of randomization/Day 1 or use of prophylactic antibiotics to prevent chronic UTIs, PVR >100 mL at screening, elevated PVR that had been treated with an intervention within 6 months, and previous or current diagnosis of prostate cancer or prostate-specific antigen (PSA) >10 ng/mL at screening.

2.3 | Outcomes

Efficacy outcomes at Week 12 during treatment Cycle 1 included the number of UI episodes per day (primary endpoint), the proportion of patients achieving ≥50% reduction in UI episodes per day, Incontinence Quality of Life Instrument (I-QOL) total score, and the proportion of patients with positive Treatment Benefit Scale (TBS) response, defined as condition "greatly improved" or "improved."[21] TBS data were pooled from studies 191622-095, 191622-520, and 191622-125 only; TBS was not assessed in study GMA-OAB-113.

The I-QOL measure consists of 22 items that are summed to obtain the total score, which is transformed to a 1- to 100-point scale, with higher scores indicating greater QOL.[22] The minimal important difference (MID) for I-QOL was defined as a ≥10-point increase. The TBS measure[21] is scored on a 4-point scale (1 = greatly improved; 2 = improved; 3 = not changed; 4 = worsened).

2.4 | Safety measures

Safety was assessed during the double-blind period by evaluating commonly reported treatment-emergent adverse events (TEAEs). TEAEs of urinary interest, including incomplete bladder emptying requiring catheterization (which is coded to "urinary retention" per MedDRA Version 26.1, the system required by regulatory authorities to categorize safety signals), hematuria, and UTI, were evaluated in treatment Cycles 1 through 4. These long-term safety data are presented for treatment Cycles 1 through 4 because fewer than 20 male patients received five or more onabotulinumtoxinA 100 U treatments. The incidence of TEAEs of urinary retention was assessed in male patients with and without BPH (as indicated by the investigator on the patient's history).

CIC was initiated in patients with PVR volume >350 mL regardless of symptoms and in patients with PVR volume ≥200 and <350 mL with symptoms that in the investigator's opinion required CIC.

2.5 | Statistical analysis

The target sample size for the pooled male population was approximately 200 patients. Demographics, baseline characteristics, and efficacy variables were analyzed in the intent-to-treat (ITT) population, defined as all randomized patients from the four studies. Safety was evaluated in the safety population, defined as all treated patients (analyzed by actual treatment received). Data were analyzed in the following subgroups based on sex and comorbid BPH status in male patients (based on investigator's clinical judgment): female patients with OAB, male patients with OAB, male patients with OAB and BPH, and male patients with OAB and without BPH. This was a post hoc analysis with pooling of studies at different times; therefore, no statistical comparisons were conducted.

3 | RESULTS

3.1 | Pooled patient population

In the pooled ITT population ($N = 1564$), there were 1370 females (87.6%) and 194 males (12.4%; Table 1). Among males, 39.2% ($n = 76$) of patients had a medical history of BPH. Demographics and baseline disease characteristics were generally similar in females and males and well balanced between the onabotulinumtoxinA and placebo groups (Table 1). Mean age was 60.4 years in females and 61.8 years in males. In the female versus male group, respectively, there was a lower proportion of patients who were ≥65 years of age (41.8% vs. 50.0%) and White (73.0% vs. 84.5%). Overall, the mean number of baseline UI episodes per day was 5.5 in females and 4.9 in males. The mean duration of OAB was longer in female versus male patients (7.0 vs. 4.8 years).

3.2 | Efficacy outcomes in treatment Cycle 1

Mean (95% confidence interval) reductions from baseline in number of UI episodes per day at Week 12 were numerically greater in the onabotulinumtoxinA 100 U group (female: −3.0 [−3.3, −2.8]; male: −2.2 [−3.0, −1.5]) versus the placebo group (female: −1.1 [−1.3, −0.8]; male: −1.3 [−1.8, −0.7]), with numerically greater improvements in females versus males (Figure 1). Improvements from baseline were observed in the onabotulinumtoxinA group irrespective of BPH status, with numerically greater improvements in patients without BPH versus those with BPH.

The proportion of patients achieving ≥50% reduction in UI episodes per day at Week 12 was numerically greater with onabotulinumtoxinA 100 U versus placebo in females and males (Figure 2). With onabotulinumtoxinA 100 U treatment, the ≥50% response rate was similar in females and males and numerically higher in males without BPH versus with BPH.

TABLE 1 Demographics and baseline OAB characteristics: ITT population.

	Males			Females		
Characteristic	**Overall ($N = 194$)**	**Placebo ($n = 96$)**	**OnabotA 100 U ($n = 98$)**	**Overall ($N = 1370$)**	**Placebo ($n = 637$)**	**OnabotA 100 U ($n = 733$)**
Age, mean (SD), years	61.8 (14.6)	60.1 (15.1)	63.5 (14.1)	60.4 (13.3)	60.4 (13.0)	60.4 (13.6)
<65 years, *n* (%)	97 (50.0)	56 (58.3)	41 (41.8)	798 (58.2)	375 (58.9)	423 (57.7)
≥65 years, *n* (%)	97 (50.0)	40 (41.7)	57 (58.2)	572 (41.8)	262 (41.1)	310 (42.3)
Race, *n* (%)						
White	164 (84.5)	84 (87.5)	80 (81.6)	1000 (73.0)	575 (90.3)	650 (88.7)
Non-White	30 (15.5)	12 (12.5)	18 (18.4)	145 (10.6)	62 (9.7)	83 (11.3)
OAB duration, mean (SD), years	4.8 (3.8)	4.9 (4.2)	4.7 (3.5)	7.0 (8.0)	6.9 (8.2)	7.0 (7.9)
UI episodes/day, mean (SD)	4.9 (3.9)	4.5 (3.7)	5.2 (4.0)	5.5 (3.5)	5.6 (3.5)	5.4 (3.5)
UUI episodes/day, mean (SD)	4.4 (3.6)	4.0 (3.5)	4.7 (3.6)	4.9 (3.3)	5.0 (3.3)	4.9 (3.2)
Micturitions/day, mean (SD)	12.4 (4.6)	12.5 (4.2)	12.4 (4.9)	11.3 (3.4)	11.1 (3.2)	11.4 (3.6)
Urgency episodes/day, mean (SD)	9.1 (5.1)	8.9 (4.8)	9.3 (5.4)	8.2 (4.0)	8.1 (3.8)	8.4 (4.1)

Abbreviations: ITT, intent-to-treat; OAB, overactive bladder; OnabotA, onabotulinumtoxinA; SD, standard deviation; UI, urinary incontinence; UUI, urgency urinary incontinence.

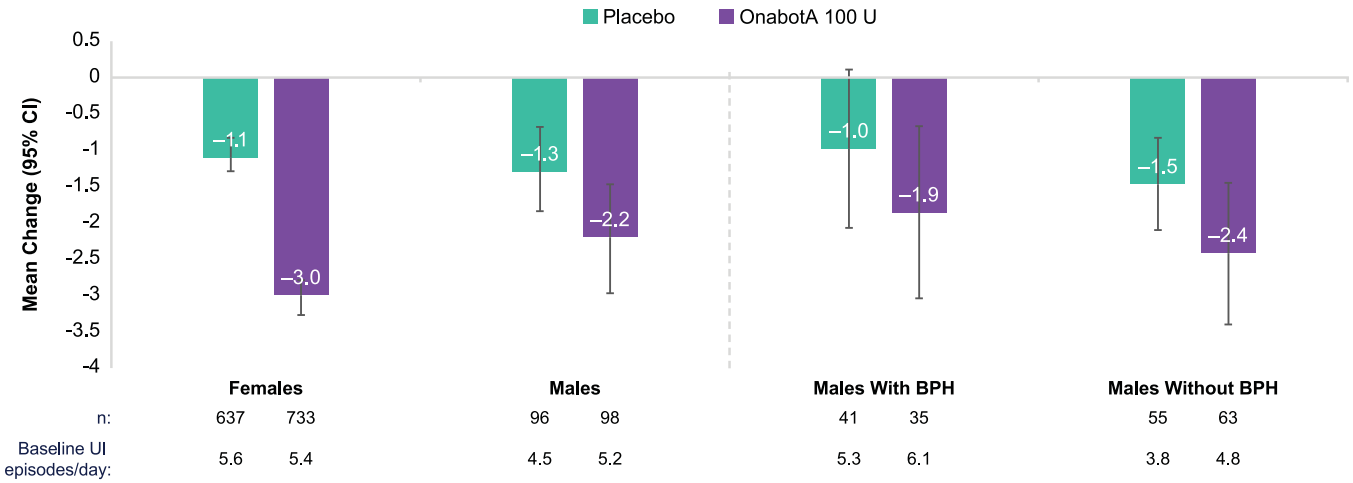

FIGURE 1 Mean change from baseline in UI episodes/day at Week 12 during treatment Cycle 1. Data are presented by sex and BPH status. Error bars represent 95% confidence intervals. BPH, benign prostatic hyperplasia; OAB, overactive bladder; OnabotA, onabotulinumtoxinA; UI, urinary incontinence.

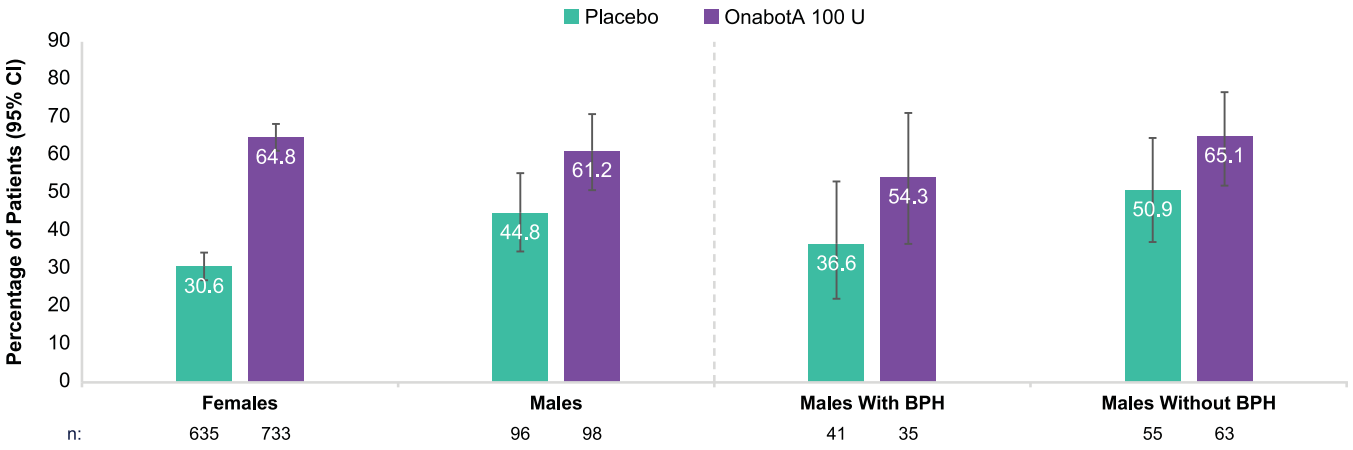

FIGURE 2 Proportion of patients achieving ≥50% reduction in UI episodes/day at Week 12 during treatment Cycle 1. Data are presented by sex and BPH status. Error bars represent 95% confidence intervals. BPH, benign prostatic hyperplasia; onabotA, onabotulinumtoxinA; OAB, overactive bladder; UI, urinary incontinence.

Mean change from baseline in I-QOL total score at Week 12 was numerically greater with onabotulinumtoxinA 100 U versus placebo in both females and males (Figure 3). Mean improvements in I-QOL total score with onabotulinumtoxinA 100 U treatment were numerically greater in females than males, and both groups exceeded the MID of a 10-point change in I-QOL total score.

The proportion of patients with positive TBS response at Week 12 was numerically greater with onabotulinumtoxinA 100 U versus placebo in females (onabotulinumtoxinA: 66.1% [400/605]; placebo: 29.7% [153/515]) and in males (onabotulinumtoxinA: 44.3% [35/79]; placebo: 27.5% [22/80]) (Figure 3). Proportions of patients with a positive TBS response were similar with onabotulinumtoxinA for males with BPH (onabotulinumtoxinA: 42.4% [14/33]; placebo: 17.9% [7/39]) and without BPH (onabotulinumtoxinA: 45.7% [21/46]; placebo: 36.6% [15/41]).

3.3 | Safety

3.3.1 | TEAEs in the first 12 weeks during treatment Cycle 1

The pooled safety population across the four studies consisted of 1552 patients with OAB, 190 males (12.2%) and 1362 females (87.8%; Table 2). Overall, 39.4% (536/1362) of females and 34.7% (66/190) of males experienced at least one TEAE in the first 12 weeks during treatment Cycle 1. The overall incidence of TEAEs was higher in females than males in both the onabotulinumtoxinA 100

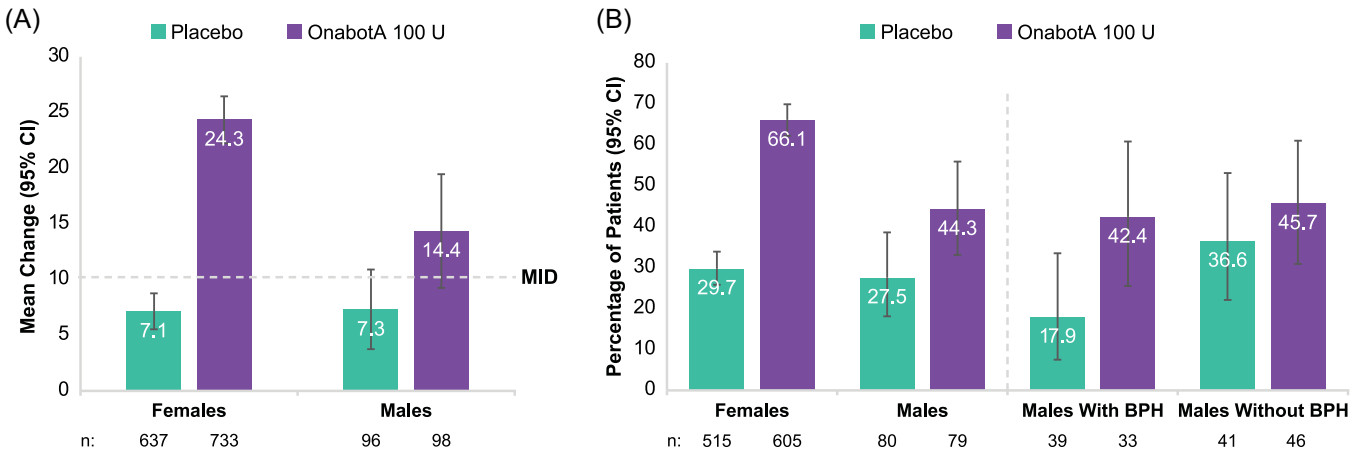

FIGURE 3 Treatment effects on health outcomes at Week 12 during treatment Cycle 1. (A) Mean change from baseline in I-QOL total score at Week 12, presented by sex. (B) Proportion of patients with positive TBS response at Week 12, presented by sex and BPH status. TBS data were pooled from studies 191622-095, 191622-520, and 191622-125 only; TBS was not assessed in study GMA-OAB-113. BPH, benign prostatic hyperplasia; I-QOL, Incontinence Quality of Life Instrument; MID, minimal important difference; onabotA, onabotulinumtoxinA; TBS, Treatment Benefit Scale; UI, urinary incontinence.

TABLE 2 Summary of frequently reported (≥3% incidence) TEAEs in the first 12 weeks during treatment Cycle 1 in female and male patients: safety population.

Females			
TEAEs in female patients, *n* (%)	**All females (*N* = 1362)**	**Placebo (*n* = 633)**	**OnabotA 100 U (*n* = 729)**
Overall	536 (39.4)	247 (39.0)	289 (39.6)
Urinary tract infection	178 (13.1)	80 (12.6)	98 (13.4)
Dysuria	66 (4.8)	22 (3.5)	44 (6.0)
Bacteriuria	49 (3.6)	25 (3.9)	24 (3.3)
Urinary retention[a]	37 (2.7)	11 (1.7)	26 (3.6)
Hematuria	15 (1.1)	3 (0.5)	12 (1.6)
Blood urine present	4 (0.3)	2 (0.3)	2 (0.3)
Males			
TEAEs in male patients, *n* (%)	**All males (*N* = 190)**	**Placebo (*n* = 94)**	**OnabotA 100 U (*n* = 96)**
Overall	66 (34.7)	35 (37.2)	31 (32.3)
Dysuria	15 (7.9)	9 (9.6)	6 (6.3)
Residual urine volume[b]	13 (6.8)	5 (5.3)	8 (8.3)
Hematuria	13 (6.8)	8 (8.5)	5 (5.2)
Urinary retention	9 (4.7)	4 (4.3)	5 (5.2)
Urinary tract infection	8 (4.2)	3 (3.2)	5 (5.2)
Pollakiuria	5 (2.6)	2 (2.1)	3 (3.1)
Blood urine present	3 (1.6)	0 (0.0)	3 (3.1)

Abbreviations: OnabotA, onabotulinumtoxinA; TEAEs, treatment-emergent adverse events.

[a]Urinary retention is defined as a temporary inability to void requiring clean intermittent catheterization (CIC). CIC was initiated in patients with post-void residual (PVR) volume >350 mL regardless of symptoms and in patients with PVR volume ≥200 and <350 mL with symptoms that in the investigator's opinion required CIC.

[b]Includes TEAEs of residual urine volume and residual urine volume increased. Incidence of this TEAE in females was 1.2% (*n* = 17) overall, 1.3% (*n* = 8) for placebo, and 1.2% (*n* = 9) for onabotA 100 U.

U and placebo groups. The most frequently reported TEAEs (≥3% incidence) in the first 12 weeks during treatment Cycle 1 in females were UTI, dysuria, bacteriuria, urinary retention, hematuria, and blood urine present; in males, they were dysuria, residual urine volume, hematuria, urinary retention, UTI, pollakiuria, and blood urine present. Overall, the incidence of UTI was higher in females (13.1%) than in males (4.2%), and hematuria was more commonly reported in males (6.8%) compared with females (1.1%).

In general, reported incidence of urinary retention was low; it was slightly lower in females compared with

males (2.7% vs. 4.7%; Table 2) and slightly higher in males with BPH (6.8%) compared to males without BPH (3.4%; Table 3). Among males with BPH, the rate of urinary retention was lower in the onabotulinumtoxinA 100 U group (5.9%) than the placebo group (7.5%). Among males without BPH, the rate of urinary retention was higher in the onabotulinumtoxinA 100 U group (4.8%) versus the placebo group (1.9%).

TABLE 3 TEAEs of urinary retention in males, by BPH status: safety population.

TEAE	Total	Placebo	OnabotA100 U
All males	$N = 190$	$n = 94$	$n = 96$
TEAEs, *n* (%)	9 (4.7)	4 (4.3)	5 (5.2)
Males with BPH	$n = 74$	$n = 40$	$n = 34$
TEAEs, *n* (%)	5 (6.8)	3 (7.5)	2 (5.9)
Males without BPH	$n = 116$	$n = 54$	$n = 62$
TEAEs, *n* (%)	4 (3.4)	1 (1.9)	3 (4.8)

Abbreviations: BPH, benign prostatic hyperplasia; OnabotA, onabotulinumtoxinA; TEAEs, treatment-emergent adverse events.

3.3.2 | Urological TEAEs of interest during treatment Cycles 1–4

Urological TEAEs of interest assessed during repeat treatments in Cycles 1–4 are summarized in Table 4. Hematuria, urinary retention, and residual urine volume occurred with a lower incidence in females versus males across most treatment cycles. The incidence of UTI was higher in females versus males across treatment Cycles 1–4. No trends indicating new safety findings were observed after repeat treatments in males or females.

4 | DISCUSSION

This pooled analysis of randomized controlled studies represents a more robust assessment of the efficacy and safety of onabotulinumtoxinA 100 U in male patients with OAB, including a larger male population ($N = 194$) than the individual trials.[17,18] In this pooled analysis, the efficacy and safety of onabotulinumtoxinA in female and male patients were consistent with previously reported findings from the Phase 3 pivotal trials.[17,18] Overall, the therapeutic

TABLE 4 Long-term safety summary: urological TEAEs of interest during treatment Cycles 1–4 in males and females: safety population.

TEAE	Treatment Cycle 1 (female: $n = 1071$; male: $n = 133$)	Treatment Cycle 2 (female: $n = 1071$; male: $n = 133$)	Treatment Cycle 3 (female: $n = 594$; male: $n = 60$)	Treatment Cycle 4 (female: $n = 448$; male: $n = 33$)
Urinary tract infection, *n* (%)				
Females	124 (11.6)	137 (12.8)	97 (16.3)	65 (14.5)
Males	3 (2.3)	4 (3.0)	0 (0.0)	0 (0.0)
Dysuria, *n* (%)				
Females	43 (4.0)	37 (3.5)	25 (4.2)	14 (3.1)
Males	7 (5.3)	6 (4.5)	1 (1.7)	0 (0.0)
Hematuria, *n* (%)				
Females	10 (0.9)	8 (0.7)	7 (1.2)	2 (0.4)
Males	7 (5.3)	6 (4.5)	1 (1.7)	1 (3.0)
Urinary retention,[a] *n* (%)				
Females	20 (1.9)	25 (2.3)	12 (2.0)	7 (1.6)
Males	5 (3.8)	5 (3.8)	1 (1.7)	2 (6.1)
Residual urine volume,[b] *n* (%)				
Females	12 (1.1)	19 (1.8)	9 (1.5)	9 (2.0)
Males	5 (3.8)	5 (3.8)	5 (8.3)	1 (3.0)

Abbreviation: TEAEs, treatment-emergent adverse events.

[a]Urinary retention is defined as a temporary inability to void requiring clean intermittent catheterization (CIC). CIC was initiated in patients with post-void residual (PVR) volume >350 mL regardless of symptoms and in patients with PVR volume ≥200 and <350 mL with symptoms that in the investigator's opinion required CIC.

[b]Includes TEAEs of residual urine volume and residual urine volume increased.

benefits of onabotulinumtoxinA 100 U included clinically meaningful improvements in the number of UI episodes per day, quality of life, and patient-reported treatment benefits in both females and males. Furthermore, improvements in UI episodes and patient-reported treatment benefits were observed in males irrespective of BPH status, with a numerically greater magnitude of improvements in males without BPH.

In this pooled analysis, the proportion of patients ≥65 years of age at baseline was numerically greater in the male versus female groups. This finding is consistent with previous research showing higher rates of OAB with UI in older men.[5] However, female patients had a numerically higher mean number of urinary incontinence episodes per day than male patients. Other OAB-related characteristics were also higher in females at baseline.

It was expected that treatment benefits would be observed in both males and females with onabotulinumtoxinA injection because the local bladder tissue does not differ between the sexes.[23] Positive treatment effects were evident in both male and female patients. However, the magnitude of treatment effects appeared to be greater in females, consistent with previous reports.[24,25] Considering there may be differences in the pathophysiology of OAB between males and females,[5,24] this discrepancy in treatment effects may reflect anatomical differences.

In this pooled analysis, the overall adverse event (AE) profile of onabotulinumtoxinA 100 U was limited to urological AEs in both males and females, consistent with a localized effect of onabotulinumtoxinA treatment in the bladder.[26] All male patients were able to spontaneously void.[27] However, the rate of incomplete bladder emptying requiring catheterization (coded to urinary retention) during treatment Cycle 1 was higher in males compared with females. These findings are consistent with a multicenter, retrospective study, in which male sex was found to be predictive of incomplete bladder emptying, and males treated with botulinum toxin A for idiopathic OAB had increased odds of urinary retention.[28] The higher rate of urinary retention observed in men may be related to male anatomy, as the prostate can contribute to voiding problems,[12] or to the fact that PVR generally increases with age,[29] and there was a greater proportion of older male patients than females in the pooled population. However, the relationship between elevated PVR and the development of symptoms requiring CIC necessitates further investigation. It should be noted that although criteria for initiating CIC were the same in all trials that were pooled in this analysis,[17–20,30] in practice, some clinicians may have different parameters for initiating CIC. Evaluating voiding efficiency in males with OAB would also be useful, as the voiding efficiency measure takes into account bladder capacity to better reflect the potential impact of elevated residual urine volume.[31,32]

In agreement with the current analysis, which found a higher overall incidence of urinary retention among males with BPH, prior research findings indicate that BPH may contribute to urinary retention.[24] In a randomized study conducted in Japan, rates of urinary retention were higher in men with higher PSA levels, which serves as a marker of elevated prostate volume.[24] However, males with BPH treated with onabotulinumtoxinA in the current study had a slightly lower rate of urinary retention than those in the placebo group. This observation may reflect relatively low sample sizes and the post hoc nature of the analysis. Also, patients with BPH may have symptoms of voiding difficulty and/or a general increased risk for retaining urine.[8,9] Patients in the study were considered to have urinary retention if they had temporary inability to void in patients with BPH regardless of treatment, as determined by the need to initiate CIC (≥200 and <350 mL with voiding symptoms or ≥350 mL regardless of symptoms). These data suggest that BPH is not a contraindication for onabotulinumtoxinA treatment; however, precaution should be taken for clinically significant bladder outlet obstruction because such patients were not included in these studies.

There were some additional differences in commonly reported TEAEs between males and females that may be considered when treating patients with onabotulinumtoxinA in clinical practice. Hematuria was more commonly reported in males, possibly related to the procedure of inserting the cystoscope through a longer urethra in males and/or placing the scope through the prostate. The rate of UTIs was higher in females, who may be more prone to developing UTIs due to risk factors related to the female anatomy, such as having a shorter urethra, certain types of birth control, or menopause.[33–36]

Overall, repeat treatment with onabotulinumtoxinA 100 U had an acceptable safety profile, with no trends of new safety findings with long-term treatment. Rates of incomplete bladder emptying requiring catheterization did not increase with subsequent treatment cycles in females, in agreement with findings from the Phase 3 extension trial (191622-096).[30] In males, there was a higher incidence of incomplete bladder emptying requiring catheterization in treatment Cycle 4 compared with earlier treatment cycles; this discrepancy may reflect the smaller sample size in the male group, particularly in later treatment cycles.

Although this pooled analysis included more male patients than prior studies, the number of females was substantially greater than the number of males, which may hinder between-group comparisons. Also, several limitations can be attributed to the post hoc nature of this

pooled analysis: no statistical analyses were performed, which restricts the interpretability of the findings, and the BPH status of patients was based on the investigator's clinical judgment as captured on the medical history case report form. Information regarding prior surgical treatment for patients with BPH is unknown. It was also not possible to analyze urodynamic parameters because such data were not captured in these studies.

5 | CONCLUSION

OnabotulinumtoxinA 100 U was efficacious and well tolerated in men and women with OAB, demonstrating clinically meaningful improvements in OAB symptoms and health outcomes. Despite a potential numerical trend toward greater benefit in women, onabotulinumtoxinA 100 U represents a valuable therapeutic option for men with OAB. No new safety issues were identified in males or females, either in the placebo-controlled treatment Cycle 1 or after repeat onabotulinumtoxinA treatment.

AUTHOR CONTRIBUTIONS

Study design: Christopher Chapple, Brenda Jenkins, Irina Yushmanova, and Victor Nitti. *Study investigator*: Christopher Chapple and Victor Nitti. *Data analysis*: Irina Yushmanova and Brenda Jenkins. *Data interpretation*: All authors. *Manuscript review and revisions*: All authors. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Victor W. Nitti is a consultant for Bright Uro, EG 247, Iota Bioscience, and Palette Life Sciences. Alfred Kohan is a consultant for AbbVie and Medtronic. Brenda Jenkins owns AbbVie stock. Kimberly Becker Ifantides is an employee of AbbVie and may hold AbbVie stock. Irina Yushmanova is an employee of AbbVie. Christopher Chapple is a consultant for AbbVie, Astellas, Bayer, and Pierre Fabre. The remaining author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/, then select "Home."

ETHICS STATEMENT

The studies complied with Good Clinical Practice regulations, and study protocols were approved by the institutional review board and/or independent ethics committee at each study site. All patients provided written informed consent before study commencement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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