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OnabotulinumtoxinA 100U provides significant improvements in overactive bladder symptoms in patients with urinary incontinence regardless of the number of anticholinergic therapies used or reason for inadequate management of overactive bladder

K.-D. Sievert,[1] C. Chapple,[2] S. Herschorn,[3] M. Joshi,[4] J. Zhou,[5] C. Nardo,[4] V. W. Nitti[6]

[1]Department of Urology, University of Tuebingen, Tuebingen, Germany
[2]Department of Urology, Royal Hallamshire Hospital, Sheffield, UK
[3]Department of Urology, University of Toronto, Toronto, ON, Canada
[4]Allergan, Inc., Irvine, CA, USA
[5]Allergan, Inc., Bridgewater, NJ, USA
[6]Department of Urology and Obstetrics and Gynecology, New York University Langone Medical Center, New York, NY, USA

Correspondence to:
Prof. Karl-Dietrich Sievert, PhD, FACS, FRCS,
Vice Chair, Professor of Urology, Director-Uro-oncology, Neurourology, Incontinence, and Reconstructive Urology, Eberhard-Karls-University, Department of Urology, University of Tuebingen, Hoppe-Seyler-Strasse 3, D72076 Tuebingen, Germany
Tel.: +49 7071 298 6611
Fax: +49 7071 295092
Email: karl.sievert@med.uni-tuebingen.de; kd_sievert@hotmail.com

Disclosures
Dr Sievert is a consultant, lecturer and trial investigator for Allergan, Inc., Astellas, AMS, Medtronic and Neotract; is a consultant for Janssen; and a lecturer and a trial investigator for Karl Storz Dr Chapple is a consultant for AMS, Lilly and ONO; and is a consultant, researcher, speaker and a trial investigator for Allergan, Inc., Astellas, Pfizer and Recordati. Dr Herschorn is a consultant and trial

SUMMARY

Introduction: A prespecified pooled analysis of two placebo-controlled, phase 3 trials evaluated whether the number of prior anticholinergics used or reason for their discontinuation affected the treatment response to onabotulinumtoxinA 100U in overactive bladder (OAB) patients with urinary incontinence (UI). **Methods:** Patients with symptoms of OAB received intradetrusor injections of onabotulinumtoxinA 100U or placebo, sparing the trigone. Change from baseline at week 12 in UI episodes/day, proportion of patients reporting a positive response ('greatly improved' or 'improved') on the treatment benefit scale (TBS), micturition and urgency were evaluated by number of prior anticholinergics (1, 2 or ≥ 3) and reason for their discontinuation (insufficient efficacy or side effects). Adverse events (AE) were assessed. **Results:** Patients had taken an average of 2.4 anticholinergics before study enrolment. OnabotulinumtoxinA reduced UI episodes/day from baseline vs. placebo, regardless of the number of prior anticholinergics (-2.82 vs. -1.52 for one prior anticholinergic; -2.58 vs. -0.58 for two prior anticholinergics; and -2.92 vs. -0.73 for three or more prior anticholinergics; all $p < 0.001$). The proportion of TBS responders was higher with onabotulinumtoxinA vs. placebo (69.0% vs. 37.2% for one prior anticholinergic; 58.8% vs. 24.8% for two prior anticholinergics and 56.4% vs. 22.5% for three or more prior anticholinergics; all $p < 0.001$). Similar results were observed regardless of the reason for discontinuation. OnabotulinumtoxinA reduced the episodes of urgency and frequency of micturition vs. placebo in all groups. AEs were well tolerated, with a comparable incidence in all groups. **Conclusion:** In patients with symptoms of OAB who were inadequately managed by one or more anticholinergics, onabotulinumtoxinA 100U provided significant and similar treatment benefit and safety profile regardless of the number of prior anticholinergics used or reason for inadequate management of OAB. **ClinicalTrials.gov:** NCT00910845, NCT00910520.

What's known
- Anticholinergics are the first-line pharmacotherapy for overactive bladder (OAB) and have been shown to reduce the symptoms of OAB and improve patients' health-related quality of life. However, many patients discontinue their use due to insufficient efficacy or intolerable side effects.
- Two large, randomised, placebo-controlled, phase 3 studies demonstrated that onabotulinumtoxinA 100U significantly decreases urinary incontinence (UI) episodes and improves patient perception of treatment, compared with placebo, in OAB patients with UI who have been inadequately managed by anticholinergic therapies.
- In a study comparing the efficacy of onabotulinumtoxinA with anticholinergic therapy, patients treated with onabotulinumtoxinA 100U were twice as likely as those receiving an anticholinergic regimen to report complete resolution of incontinence episodes.

What's new
- Regardless of the number of prior anticholinergics used or reason for their discontinuation, treatment with onabotulinumtoxinA 100U significantly reduced UI, urgency episodes and micturition frequency, which was reflected in patients' positive perception of treatment benefit.
- Results of the subgroup analyses were similar to the significant and clinically relevant improvements seen in the overall pooled population.
- OnabotulinumtoxinA was well tolerated, with no clinically relevant differences in the incidence of adverse events between the overall pooled population and the subgroups.

Introduction

Overactive bladder (OAB) is a chronic symptom complex affecting 12–17% of the general population (1–3), and is characterised by urgency, with or without urinary urgency incontinence (UUI) usually with increased daytime frequency and nocturia (4). Urinary incontinence (UI) and other associated

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symptoms of OAB can be debilitating for affected patients and may have a profound negative effect on patients' health-related quality of life (5,6). In addition, urgency is rated by patients in some studies as the most bothersome of all symptoms, causing distress, embarrassment, loss of independence and disruption in their daily lives (7).

Anticholinergic agents are considered the mainstay of pharmacologic therapy for OAB. Randomised controlled trials of several anticholinergic therapies have demonstrated clinical benefit, including improvements in the symptoms of OAB and health-related quality of life (8). However, up to 70% of individuals discontinue anticholinergic therapy within a year of initiation (9–12), most commonly due to inadequate efficacy and/or intolerable side effects (12). Patients who continue anticholinergic therapy often have to try multiple anticholinergic agents in succession (11).

Since OAB is a chronic symptom complex requiring long-term therapy, there is a need for alternative therapeutic options that are effective and could potentially maximise the chance of treatment success in patients who are inadequately managed by their current therapy. OnabotulinumtoxinA is the only botulinum toxin approved for the treatment of OAB in patients, who have been inadequately managed by ≥ 1 anticholinergic therapy. Units of biological activity of onabotulinumtoxinA cannot be compared with or converted into units of any other botulinum toxin product, and onabotulinumtoxinA is not interchangeable with other botulinum toxin preparations.

Two large, double-blind, placebo-controlled, phase 3 trials (13–15) showed that onabotulinumtoxinA 100U significantly reduces all symptoms of OAB, including episodes of incontinence, urgency, micturition and nocturia compared with placebo. Furthermore, 22.9% and 31.4% (15) of onabotulinumtoxinA-treated patients achieved complete continence at week 12 (i.e. 100% reduction in UI episodes) in each of the trials (13,15), compared with only 6.5% and 10.3% of patients in the respective placebo groups. Reductions in OAB symptoms were also reflected in clinically meaningful improvements in patients' health-related quality of life.

Given the potential for cycling of patients on different anticholinergic regimens, and the high discontinuation rates for anticholinergics, it is important to determine if onabotulinumtoxinA provides a similar clinical benefit and safety profile regardless of the number of prior anticholinergics used or the reason for their inadequate management of OAB. This prespecified pooled analysis evaluated the efficacy and safety of onabotulinumtoxinA in the two following subgroups of patients: by the number of prior anticholinergics used and by reason for discontinuation of anticholinergic therapy. Pooling the data from the two phase 3 trials (13,14) provides a larger dataset for examination of the efficacy and safety profile demonstrated in the individual studies. The pooled data also allows for further analyses of treatment response to onabotulinumtoxinA 100U in OAB patients with UI, who had previously used one or more anticholinergics or had discontinued their use due to inadequate efficacy or intolerable side effects.

investigator for Allergan, Inc., Astellas and Pfizer; and a consultant for Lilly, Promedon and Merus. Drs Joshi, Zhou and Nardo are employees of Allergan, Inc. Dr Nitti is a consultant, lecturer and investigator for Allergan, Inc.; is a consultant and investigator for Astellas and AMS; is a consultant for Coloplast, Serenity, Medtronic, ONO, Ipsen, Theracoat and Pneumoflex; and has an investment interest in Serenity.

Methods

Study design

Details on the two phase 3 placebo-controlled trials (NCT00910845 and NCT00910520) have been previously published (13,14). Briefly, patients with idiopathic OAB with three or more UUI episodes over a 3-day period and eight or more micturitions/day were randomised 1 : 1 to receive 20 cystoscopic intradetrusor injections (0.5 ml/injection) of onabotulinumtoxinA 100U or placebo, sparing the trigone.

Patients were inadequately managed by one or more anticholinergic (insufficient efficacy or intolerable side effects); those with a predominance of stress UI were excluded. The number of prior anticholinergic therapies used and the reason for their inadequate management of OAB were recorded. Patients participated in the study for 24 weeks unless they withdrew consent or retreatment occurred. Retreatment was with onabotulinumtoxinA, and could occur from 12 weeks onward if the patient requested it and had at least two UUI episodes over 3 days. Therefore, the true placebo-controlled period was 12 weeks. The period between receipt of initial treatment and retreatment or study exit (if no retreatment) was defined as treatment cycle 1.

Efficacy and safety evaluations

A 3-day paper bladder diary was used to collect all OAB symptoms (episodes of incontinence, urgency and micturition). Patients recorded their perception of treatment benefit at each posttreatment visit using the treatment benefit scale (TBS), rating their condition as 'greatly improved', 'improved', 'not changed' or 'worsened'. The number of prior anticholinergics used and the reasons for inadequate management by anticholinergic therapy were also recorded.

The coprimary end-points of change from baseline at week 12 in UI episodes/day and proportion of patients reporting a positive response (rating their condition 'greatly improved' or 'improved') on the TBS were evaluated in the overall pooled population and in subgroups of patients by number of prior

anticholinergic therapies (1, 2 or ≥ 3) and the primary reason for inadequate management by their first anticholinergic therapy (insufficient efficacy or intolerable side effects). Change from baseline in urgency episodes and micturition frequency was also assessed. The time to patient request for retreatment was recorded for assessment of duration of treatment.

Adverse events (AEs), postvoid residual (PVR) urine volume and use of clean intermittent catheterisation (CIC) were evaluated at weeks 2, 6 and 12 posttreatment or at any other time depending on clinical need. CIC was initiated if the PVR urine volume was ≥ 200 ml and < 350 ml with associated symptoms (e.g. voiding difficulties or sensation of bladder fullness) or if the PVR urine volume was ≥ 350 ml, regardless of symptoms. The AE of urinary retention was defined as a PVR urine volume ≥ 200 ml that required CIC. The AE of urinary tract infection (UTI) was defined as positive urine culture with bacteriuria count of $> 10^5$ colony-forming units/ml, together with leukocyturia of > 5/high power field, even in the absence of symptoms.

Statistical methods

Efficacy analyses were conducted using the overall pooled intent-to-treat population (all randomised patients) and safety analyses used the safety population, which comprised all patients who received treatment analysed by actual treatment received.

Daily UI episodes were analysed using an analysis of covariance model, with baseline number of UI episodes as covariates and study site and treatment group as factors. TBS was analysed using the Cochran-Mantel-Haenszel χ^2 method with the number of baseline urgency UI episodes (≤ 9 or > 9) as a stratification factor. Both phase 3 studies were planned to provide 80% overall power to detect a between-group difference in change from baseline in the co-primary study end-points (a difference of 2.3 UI episodes/day, with a standard deviation of 8.5 for UI and a between-group difference of 22% for TBS), assuming an alpha of 0.05.

Results

Baseline demographics, disease characteristics and anticholinergic profile

The overall pooled population comprised 1105 patients randomised to onabotulinumtoxinA 100U ($n = 557$) or placebo ($n = 548$). Baseline demographics, disease characteristics and prior anticholinergic therapy profiles were balanced between the treatment groups (Table 1).

The average age of patients was 60.4 years; 87.8% were females. The mean duration of OAB was 6.1 years, and patients reported an average of 5.4 UI episodes/day. Patients had used an average of 2.4 anticholinergics prior to study entry; 34.5% (378/1097) of patients had previously used one anticholinergic therapy, 27.0% (296/1097) had used two and 38.6% (423/1097) had used three or more anticholinergic therapies. The mean duration of prior anticholinergic use was approximately 2.3 years (Table 1).

Overall, 3407 unique regimens of anticholinergic therapies were taken by all patients prior to study enrolment. The majority (82.2%) of these therapies provided insufficient efficacy. For 70.2% of patients, insufficient efficacy was the primary reason for inadequate management by all of their prior anticholinergic therapies, for 10.3% of patients, the primary reason was intolerable side effects, and 19.2% of patients discontinued at least one anticholinergic for inadequate efficacy and at least one anticholinergic for intolerable side effects (Table 1). The primary reason for inadequate management by the first anticholinergic was used for analysis.

Efficacy outcomes

Overall pooled population

Treatment with onabotulinumtoxinA 100U resulted in significant reductions from baseline in daily UI episodes at week 12 compared with placebo (−2.80 vs. −0.95 episodes/day; $p < 0.001$) (Figure 1A). Significantly higher proportions of onabotulinumtoxinA- than placebo-treated patients demonstrated a ≥ 50% reduction from baseline in UI episodes (60.5% vs. 31.0%; $p < 0.001$) and became continent (100% reduction in UI episodes; 27.1% vs. 8.4%; $p < 0.001$) (Figure 1B). At week 12, a significantly greater proportion of onabotulinumtoxinA-treated patients achieved a positive response on the TBS compared with placebo (61.8% vs. 28.0%; $p < 0.001$) (Figure 2).

Improvements were also demonstrated in other OAB symptoms following treatment with onabotulinumtoxinA compared with placebo, with significant reductions from baseline at week 12 in the average daily episodes of urgency (−3.30 vs. −1.23; $p < 0.001$) (Figure 3A) and micturition (−2.35 vs. −0.87; $p < 0.001$) (Figure 3B).

The duration of treatment effect (median time to qualification for retreatment) was 24 weeks following treatment with onabotulinumtoxinA compared with 13 weeks with placebo. Retreatment could occur from 12 weeks onward, thus, the placebo-treated patients requested/received retreatment shortly after it was permitted.

Table 1 Baseline demographics, disease characteristics and ACH profile (overall pooled ITT population)

Characteristic	Placebo (*n* = 548)	OnabotA 100U (*n* = 557)	Overall (*N* = 1105)
Age (years)	60.1 ± 13.6	60.6 ± 14.2	60.4 ± 13.9
Female gender, *n* (%)	474 (86.5)	496 (89.0)	970 (87.8)
Duration of OAB (years)	6.1 ± 7.1	6.0 ± 7.1	6.1 ± 7.1
Daily UI episodes	5.4 ± 3.6	5.5 ± 3.7	5.4 ± 3.6
Daily urgency episodes	8.3 ± 4.1	8.8 ± 4.7	8.6 ± 4.4
Daily micturition episodes	11.5 ± 3.4	12.0 ± 4.1	11.7 ± 3.9
PVR urine volume (ml)	19.5 ± 24.7	22.5 ± 27.4	21.0 ± 26.1
Number of prior ACH therapies used by patients			
Overall mean number	2.5	2.4	2.4
1 ACH therapy, *n*/*N* (%)	176/545 (32.3)	202/552 (36.6)	378/1097* (34.5)
2 ACH therapies, *n*/*N* (%)	145/545 (26.6)	151/552 (27.4)	296/1097* (27.0)
≥ 3 ACH therapies, *n*/*N* (%)	224/545 (41.1)	199/552 (36.1)	423/1097* (38.6)
Mean duration of ACH use (years)	2.2	2.4	2.3
Reason for inadequate management of OAB by ACH therapies			
Overall unique regimens of ACH therapies across all patients, *n*/*N* (%)			
Insufficient efficacy	1273/1576 (80.8)	1233/1471 (83.8)	2506/3047 (82.2)
Side effects	303/1576 (19.2)	238/1471 (16.2)	541/3047 (17.8)
Number of patients inadequately managed by ACH therapies, *n*/*N* (%)			
Only insufficient efficacy	372/547 (68.0)	402/555 (72.4)	774/1102† (70.2)
Only side effects	56/547 (10.2)	58/555 (10.5)	114/1102† (10.3)
Both‡ (insufficient efficacy and side effects)	119/547 (21.8)	93/555 (16.8)	212/1102† (19.2)

Data are mean ± SD unless otherwise indicated. *Eight patients had missing information regarding prior ACH use. †Three patients had missing information regarding reason for discontinuation of ACH therapy. ‡Patients who had discontinued at least one ACH for inadequate efficacy and at least one ACH for intolerable side effects. ACH, anticholinergic; ITT, intent-to-treat; OAB, overactive bladder; onabotA, onabotulinumtoxinA; PVR, postvoid residual.

Subgroup of patients by number of prior anticholinergics used (1, 2 and ≥ 3)

As in the overall pooled population, significant and meaningful reductions from baseline in daily UI episodes were observed with onabotulinumtoxinA compared with placebo regardless of the number of prior anticholinergics used. At week 12, mean reductions were −2.82 vs. −1.52 for the subgroup with one prior anticholinergic, −2.58 vs. −0.58 for those with two prior anticholinergics and −2.92 vs. −0.73 for the three or more anticholinergics subgroup ($p < 0.001$ vs. placebo for all) (Figure 1A).

These results were reflected in the patient perception of benefit with 69.0%, 58.8% and 56.4% of onabotulinumtoxinA-treated patients with one, two and three or more prior anticholinergics, respectively, reporting a positive TBS response, compared with only 37.2%, 24.8% and 22.5% of patients in the respective placebo groups ($p < 0.001$ vs. placebo for all) (Figure 2).

Significant reductions, comparable with the overall pooled population, were also observed in the OAB symptoms of urgency and micturition in onabotulinumtoxinA- vs. placebo-treated patients, regardless of the number of prior anticholinergic therapies used. Reductions from baseline in average daily episodes of urgency with onabotulinumtoxinA compared with placebo were −3.63 vs. −1.97 for patients with one prior anticholinergic, −3.37 vs. −0.82 for those with two prior anticholinergics and −2.90 vs. −0.93 for patients with three or more prior anticholinergics ($p < 0.001$ vs. placebo for all) (Figure 3A). Reductions from baseline in mean daily episodes of micturition were −2.70 vs. −1.45 for the subgroup with one prior anticholinergic, −2.41 vs. −0.71 for those with two prior anticholinergics and −1.93 vs. −0.52 for patients with three or more prior anticholinergics ($p < 0.001$ vs. placebo for all) (Figure 3B).

Subgroup of patients by reasons for inadequate management by anticholinergic therapy (inadequate efficacy and intolerant side effects)

OnabotulinumtoxinA significantly reduced UI episodes from baseline compared with placebo at week 12, regardless of the reason for inadequate management of OAB by anticholinergic therapy. Reductions from baseline were −2.80 vs. −0.99 episodes/day in the onabotulinumtoxinA and placebo groups, respectively, for patients with insufficient efficacy ($p < 0.001$) and −2.68 vs. −0.71 episodes/day for those with intolerable side effects ($p < 0.05$) (Figure 1A).

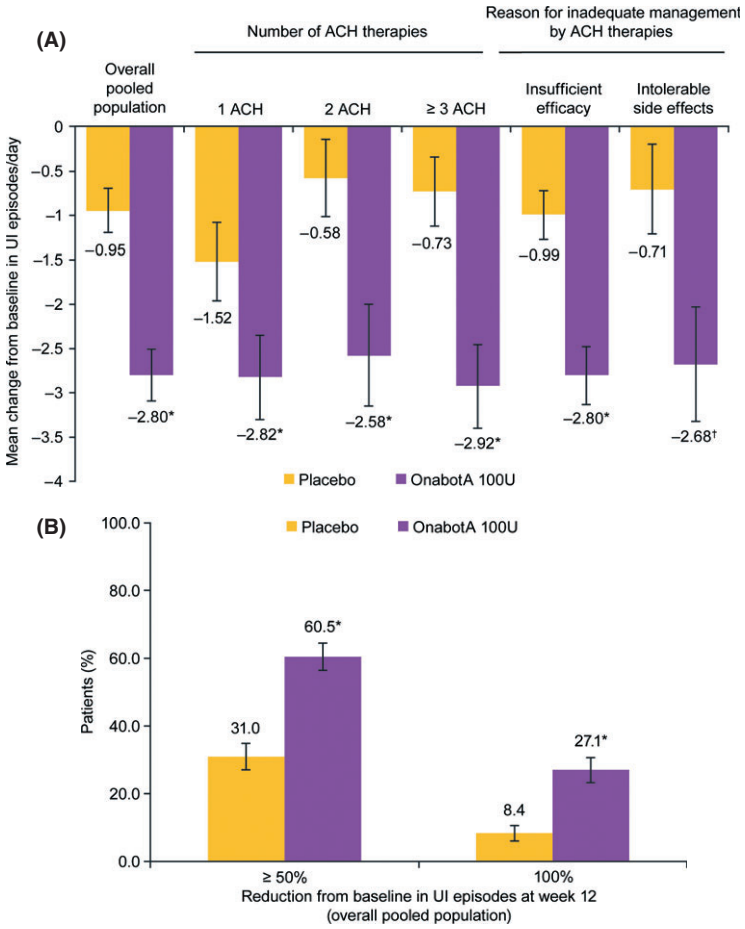

Figure 1 (A) Change from baseline in daily average UI episodes at week 12 in the overall pooled population and subgroups, and (B) proportion of patients achieving ≥ 50% or 100% reduction from baseline in UI episodes at week 12 in the overall pooled population. Error bars are 95% ± CI. *$p < 0.001$; †$p < 0.05$ vs. placebo. ACH, anticholinergic; CI, confidence interval; onabotA, onabotulinumtoxinA; UI, urinary incontinence.

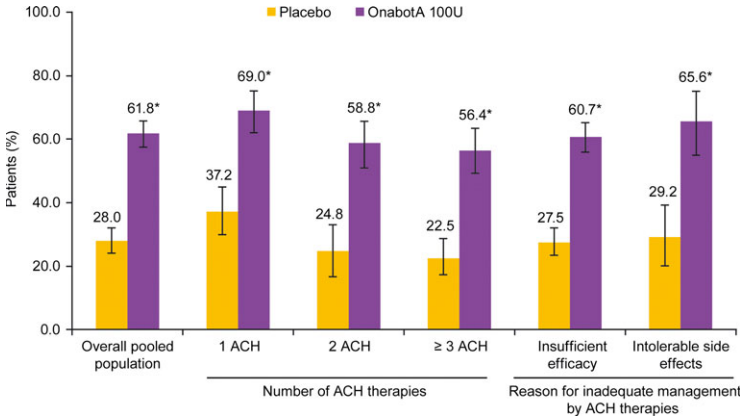

Figure 2 Proportion of patients with a positive response (their condition 'greatly improved' or 'improved') on the treatment benefit scale at week 12 in the overall pooled population and subgroups. Error bars are 95% ± CI. *$p < 0.001$ vs. placebo. ACH, anticholinergic; CI, confidence interval; onabotA, onabotulinumtoxinA.

A significantly higher proportion of patients with insufficient efficacy reported a positive response on the TBS following treatment with onabotulinumtoxinA 100U compared with placebo (60.7% vs. 27.5%; $p < 0.001$). Similarly, the proportion of TBS responders was higher in the onabotulinumtoxinA

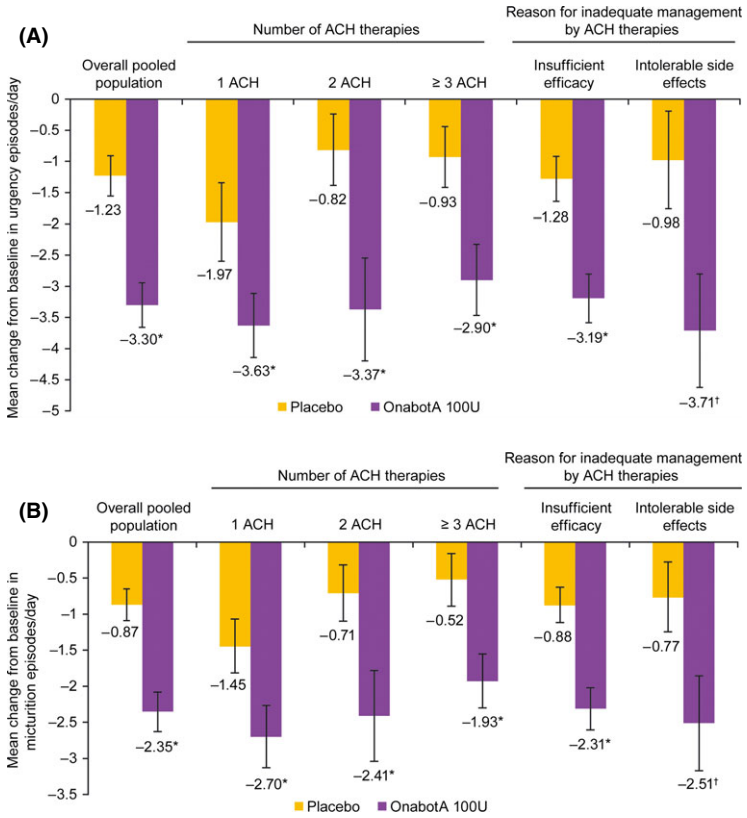

Figure 3 Change from baseline in daily average episodes of (A) urgency and (B) micturition at week 12 in the overall pooled population and subgroups. Error bars are 95% ± CI. *$p < 0.001$; †$p < 0.05$ vs. placebo. ACH, anticholinergic; CI, confidence interval; onabotA, onabotulinumtoxinA.

group compared with placebo in the subgroup of patients with intolerable side effects (65.6% vs. 29.2%; $p < 0.001$) (Figure 2).

Overactive bladder symptoms of urgency and micturition were significantly reduced with onabotulinumtoxinA treatment compared with placebo, regardless of the reason for inadequate management of OAB. At week 12, reductions from baseline in mean daily episodes of urgency were −3.19 vs. −1.28 for patients with insufficient efficacy ($p < 0.001$) and −3.71 vs. −0.98 ($p < 0.05$) for those with intolerable side effects (Figure 3A). Reductions from baseline in mean daily episodes of micturition were −2.31 vs. −0.88 ($p < 0.001$) in patients with insufficient efficacy and −2.51 vs. −0.77 ($p < 0.05$) in those with intolerable side effects (Figure 3B). These reductions in the episodes of urgency and micturition frequency were comparable with the results observed in the pooled population (Figure 3A and B).

Safety outcomes

The most common AEs were localised urologic events. UTI was the most frequently reported AE in the pooled safety population (25.5% with onabotulinumtoxinA vs. 9.6% with placebo) (Table 2) and all but one case of UTI was uncomplicated; one case of pyelonephritis was reported in the onabotulinumtoxinA group. Other AEs of note that occurred at a higher incidence with onabotulinumtoxinA than placebo at any time in treatment cycle 1 were dysuria (10.9% vs. 7.0%), bacteriuria (8.0% vs. 3.5%) and urinary retention (5.8% vs. 0.4%). There were no clinically relevant differences in the incidence of AEs in the pooled population and the subgroups.

The majority of patients in both the onabotulinumtoxinA (82.3%) and placebo group (95.7%) had a PVR urine volume of ≤ 100 ml at week 12 in treatment cycle 1 (Table 3).

In the pooled safety population, the proportion of patients who initiated CIC at any time in treatment cycle 1 was low: 6.5% (36/552) in the onabotulinumtoxinA 100U group vs. 0.4% (2/542) in the placebo group (Table 3). Following treatment with onabotulinumtoxinA, 2.5% (14/552) of the patients used CIC for ≤ 6 weeks, and 2.7% (15/552) used CIC for > 12 weeks (Figure 4). Nearly all patients in the onabotulinumtoxinA group (20/21; 95.2%) in the

Table 2 AEs in the pooled safety population and subgroups by number of prior ACHs used and primary reason for inadequate management of OAB by ACH therapy in treatment cycle 1

	Number of prior ACH therapies								Reason for inadequate management			
	Overall pooled		1 ACH		2 ACH		≥ 3 ACH		Insufficient efficacy		Intolerable side effects	
AE, *n* (%)	Pbo (*n* = 542)	OnabotA (*n* = 552)	Pbo (*n* = 173)	OnabotA (*n* = 199)	Pbo (*n* = 145)	OnabotA (*n* = 148)	Pbo (*n* = 223)	OnabotA (*n* = 203)	Pbo (*n* = 445)	OnabotA (*n* = 454)	Pbo (*n* = 96)	OnabotA (*n* = 94)
AEs with incidence ≥ 3%												
UTI*	52 (9.6)	141 (25.5)	16 (9.2)	43 (21.6)	5 (3.4)	40 (27.0)	30 (13.5)	49 (24.1)	44 (9.9)	113 (24.9)	7 (7.3)	18 (19.1)
Dysuria	38 (7.0)	60 (10.9)	14 (8.1)	11 (5.5)	15 (10.3)	16 (10.8)	9 (4.0)	29 (14.3)	30 (6.7)	43 (9.5)	8 (8.3)	13 (13.8)
Bacteriuria	19 (3.5)	44 (8.0)	7 (4.0)	12 (6.0)	7 (4.8)	16 (10.8)	4 (1.8)	11 (5.4)	15 (3.4)	32 (7.0)	3 (3.1)	7 (7.4)
Haematuria	18 (3.3)	18 (3.3)	7 (4.0)	9 (4.5)	6 (4.1)	2 (1.4)	5 (2.2)	7 (3.4)	12 (2.7)	13 (2.9)	6 (6.3)	5 (5.3)
Urinary retention†	2 (0.4)	32 (5.8)	2 (1.2)	7 (3.5)	0 (0)	8 (5.4)	0 (0)	16 (7.9)	2 (0.4)	25 (5.5)	0 (0)	6 (6.4)
Residual urine volume	2 (0.4)	19 (3.4)	1 (0.6)	7 (3.5)	1 (0.7)	4 (2.7)	0 (0)	8 (3.9)	2 (0.4)	13 (2.9)	0 (0)	6 (6.4)
Sinusitis	6 (1.1)	18 (3.3)	4 (2.3)	6 (3.0)	0 (0)	4 (2.7)	2 (0.9)	7 (3.4)	5 (1.1)	16 (3.5)	1 (1.0)	1 (1.1)
Leukocyturia	2 (0.4)	18 (3.3)	1 (0.6)	4 (2.0)	1 (0.7)	5 (3.4)	0 (0)	6 (3.0)	2 (0.4)	12 (2.6)	0 (0)	3 (3.2)
Diarrhoea	9 (1.7)	12 (2.2)	3 (1.7)	4 (2.0)	1 (0.7)	0 (0)	5 (2.2)	7 (3.4)	6 (1.3)	10 (2.2)	3 (3.1)	1 (1.1)
Nasopharyngitis	12 (2.2)	14 (2.5)	3 (1.7)	1 (0.5)	3 (2.1)	6 (4.1)	6 (2.7)	3 (1.5)	11 (2.5)	8 (1.8)	1 (1.0)	2 (2.1)
Back pain	9 (1.7)	9 (1.6)	3 (1.7)	1 (0.5)	5 (3.4)	2 (1.4)	0 (0)	4 (2.0)	7 (1.6)	5 (1.1)	1 (1.0)	2 (2.1)
Study discontinuations	69 (12.7)	59 (10.7)	25 (14.5)	21 (10.6)	20 (13.8)	18 (12.2)	24 (10.8)	19 (9.4)	58 (13.0)	51 (11.2)	11 (11.5)	7 (7.4)
Due to AEs	9 (1.7)	8 (1.4)	4 (2.3)	1 (0.5)	2 (1.4)	2 (1.4)	3 (1.3)	5 (2.5)	9 (2.0)	7 (1.5)	0 (0)	1 (1.1)
Other reasons	6 (1.1)	4 (0.7)	3 (1.7)	0 (0)	3 (2.1)	1 (0.7)	0 (0)	3 (1.5)	4 (0.9)	4 (0.9)	2 (2.1)	0 (0)

*Defined as a positive urine culture with bacteriuria count of $> 10^5$ colony-forming units/ml together with leukocyturia of > 5/high power field and not limited to symptomatic patients only. †Defined as PVR urine ≥ 200 ml that required CIC. ACH, anticholinergic; AEs, adverse events; CIC, clean intermittent catheterisation; onabotA, onabotulinumtoxinA; pbo, placebo; PVR, postvoid residual; UTI, urinary tract infection.

Table 3 Proportion of patients with absolute PVR urine volume by different thresholds, and patients initiating CIC, both overall and by maximum attained PVR urine volume during treatment cycle 1

	Number of prior ACH therapies								Reason for inadequate management			
	Overall pooled		1 ACH		2 ACH		≥ 3 ACH		Insufficient efficacy		Intolerable side effects	
	Pbo (*n* = 514)	OnabotA (*n* = 526)	Pbo (*n* = 162)	OnabotA (*n* = 190)	Pbo (*n* = 140)	OnabotA (*n* = 144)	Pbo (*n* = 211)	OnabotA (*n* = 190)	Pbo (*n* = 423)	OnabotA (*n* = 433)	Pbo (*n* = 90)	OnabotA (*n* = 89)
Proportion of patients with absolute PVR urine volumes at week 12 by different thresholds, *n* (%)												
≤ 100 ml	492 (95.7)	433 (82.3)	157 (96.9)	159 (83.7)	131 (93.6)	122 (84.7)	203 (96.2)	151 (79.5)	406 (96.0)	362 (83.6)	85 (94.4)	68 (76.4)
> 100 and < 200 ml	20 (3.9)	76 (14.4)	5 (3.1)	26 (13.7)	8 (5.7)	18 (12.5)	7 (3.3)	31 (16.3)	15 (3.5)	57 (13.2)	5 (5.6)	18 (20.2)
≥ 200 and < 350 ml	2 (0.4)	13 (2.5)	0 (0)	5 (2.6)	1 (0.7)	3 (2.1)	1 (0.5)	5 (2.6)	2 (0.5)	12 (2.8)	0 (0)	1 (1.1)
≥ 350 ml	0 (0)	4 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	3 (1.6)	0 (0)	2 (0.5)	0 (0)	2 (2.2)
Proportion of patients initiating CIC at any time in treatment cycle 1, *n/N* (%)												
Overall	2/542 (0.4)	36/552 (6.5)	1/173 (0.6)	8/199 (4.0)	1/145 (0.7)	10/148 (6.8)	0/223 (0)	17/203 (8.4)	2/445 (0.4)	27/454 (5.9)	0/96 (0)	8/94 (8.5)
Proportion of patients initiating CIC by maximum attained PVR urine volume at any time in treatment cycle 1, *n/N* (%)												
≤ 100 ml	1/477 (0.2)	1/332 (0.3)	0/154 (0)	0/128 (0)	1/127 (0.8)	0/92 (0)	0/195 (0)	1/113 (0.9)	1/392 (0.3)	1/282 (0.4)	0/84 (0)	0/47 (0)
> 100 and < 200 ml	0/60 (0)	2/161 (1.2)	0/18 (0)	1/55 (1.8)	0/17 (0)	1/43 (2.3)	0/26 (0)	0/61 (0)	0/49 (0)	1/126 (0.8)	0/11 (0)	1/35 (2.9)
≥ 200 and < 350 ml	0/4 (0)	13/38 (34.2)	NA	2/11 (18.2)	0/1 (0)	2/6 (33.3)	0/2 (0)	9/21 (42.9)	0/3 (0)	12/32 (37.5)	0/1 (0)	1/6 (16.7)
≥ 350 ml	1/1 (100.0)	20/21 (95.2)	1/1 (100.0)	5/5 (100.0)	NA	7/7 (100.0)	NA	7/8 (87.5)	1/1 (100.0)	13/14 (92.9)	NA	6/6 (100.0)

ACH, anticholinergic; CIC, clean intermittent catheterisation; NA, not available; onabotA, onabotulinumtoxinA; pbo, placebo; PVR, postvoid residual.

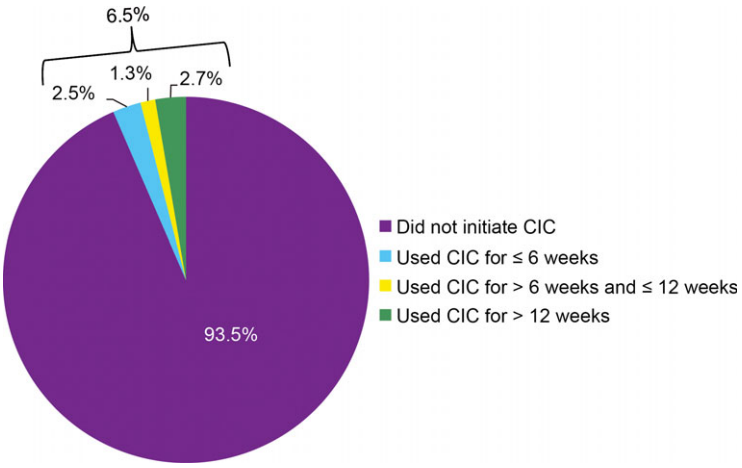

Figure 4 Duration of CIC in the pooled safety population. CIC was initiated when PVR ≥ 350 ml, or if PVR ≥ 200 ml and < 350 ml and patient had associated symptoms assessed by the investigator to require CIC, or when PVR ≥ 350 ml regardless of symptoms. CIC, clean intermittent catheterisation; PVR, postvoid residual.

overall pooled population who had a PVR urine volume ≥ 350 ml initiated CIC, while 13/38 patients (34.2%) with PVR urine volumes between 200 and < 350 ml initiated CIC (Table 3).

Similar to the overall pooled safety population, the rates of CIC initiation were low in the subgroup by number of prior anticholinergics and reason for discontinuation of anticholinergics (Table 3).

Study discontinuation rates due to AEs were low in the overall pooled safety population: 1.4% in the onabotulinumtoxinA group and 1.7% in the placebo group; comparable rates of discontinuations due to AEs were observed in the subgroups (Table 2). Overall, two deaths, both unrelated to treatment, were reported during treatment cycle 1. One patient in the placebo group died due to diverticulitis and pneumothorax and another patient treated with onabotulinumtoxinA 100U died of an acute myocardial infarction.

Discussion

This prespecified pooled analysis of two phase 3, randomised, placebo-controlled trials in OAB patients with UI demonstrates that regardless of the number of prior anticholinergic medications used or the reasons for inadequate management of OAB, onabotulinumtoxinA 100U provides significant and clinically meaningful improvements in the symptoms of OAB, including episodes of incontinence, urgency and micturition. These findings are clinically relevant, particularly since the persistence rates for anticholinergic therapy are low (16–18), and as many as 70% of OAB patients discontinue treatment within a year of initiation either due to insufficient efficacy or intolerable side effects (9–12).

There is limited information on the benefits of switching to another anticholinergic agent after prior treatment failure, and the few studies that have reported efficacy after switching were open-label, non-randomised trials and thus were subject to patient and physician bias (19,20). Furthermore, a recent study showed that patients treated with a single injection of onabotulinumtoxinA 100U were twice as likely as those receiving an anticholinergic regimen (that allowed for dose escalation and switching of anticholinergic therapy) to report complete resolution of UUI episodes (21).

Findings in our analysis demonstrate that onabotulinumtoxinA is an effective alternative in OAB patients after failing treatment with just one anticholinergic agent. Hence, these results may have important implications for clinical practice and help physicians make informed decisions about second-line treatment options for their patients.

Furthermore, onabotulinumtoxinA was similarly effective in patients who discontinued prior anticholinergic therapy due to inadequate efficacy or intolerable side effects. In contrast to our results, a small, retrospective study reported that patients who were intolerant to anticholinergic side effects had a more successful treatment response to onabotulinumtoxinA than those who had inadequate efficacy (22). However, the treatment success reported in the retrospective study may be subject to response bias, as it was solely based on patient satisfaction and did not consider objective efficacy assessments.

Results of the subgroup analyses of patients by number of prior anticholinergics and reasons for discontinuation of anticholinergics were similar to the significant and clinically relevant improvements seen in the overall pooled population. This is notable

since it demonstrates that regardless of the number of anticholinergics failed or the reason for failure, patients have the potential to benefit from onabotulinumtoxinA therapy, with significant improvements in OAB symptoms.

Some studies have shown that among symptoms of OAB, urgency appears to have the greatest negative impact on patients' health-related quality of life (7), and thus has been described as the core symptom of OAB (23,24). Urgency was the strongest predictor of OAB-associated bother and patients with urgency were more likely to have worse scores on health-related quality of life, anxiety and depression assessments than patients without urgency (25). In this analysis, treatment with onabotulinumtoxinA significantly reduced the number of urgency episodes in all groups that were studied. The improvements noted in urgency and other OAB symptoms corresponded to the patient perception of treatment benefit, with as many as 60–70% of the patients reporting a significant improvement in their condition following treatment with onabotulinumtoxinA, both in the subgroups and the pooled population.

The robust efficacy of onabotulinumtoxinA could be attributed to dual efferent and afferent inhibitory effects on pathways of bladder control. By directly inhibiting the efferent acetylcholine-mediated detrusor contractions, onabotulinumtoxinA contributes to the reductions in leakage due to episodes of incontinence. In addition, injection of onabotulinumtoxinA into the bladder wall decreases the mucosal levels of the afferent neuronal receptors TRPV1 and P2X3, which are important in sensory feedback (26–29), and may decrease the levels of afferent neurotransmitters relevant to the sensation of urgency. Thus, the current notion is that onabotulinumtoxinA modulates the intrinsic reflexes thought to cause the OAB condition and improves the associated symptoms of OAB, including the most bothersome symptom of urgency.

The duration of treatment effect (median time to qualification for retreatment) with onabotulinumtoxinA was significantly longer compared with placebo (24 vs. 13 weeks, respectively). An interim analysis of an ongoing study of repeated treatments with onabotulinumtoxinA showed sustained and consistent improvements in OAB symptoms, patients' perception of improvement in their condition and health-related quality of life (30). Taken together, these results suggest that onabotulinumtoxinA could potentially maximise the chance of treatment success and long-term adherence to therapy in OAB patients who are inadequately managed by anticholinergics. These results are noteworthy considering that the majority of OAB patients discontinue anticholinergic therapy in a median of < 20 weeks of starting treatment (11).

The pooled safety results confirm those observed in the individual phase 3 trials (13,14), indicating that onabotulinumtoxinA was well tolerated, with most of the AEs localised to the urinary tract. In addition, there were no clinically relevant differences in the incidence of AEs between the subgroups and the pooled population. Although onabotulinumtoxinA was associated with an increase in PVR urine volume in all groups, the clinical consequence of this increase was limited, as the rates of urinary retention (range: 3.5–7.9%) and initiation of CIC were low (range: 4.0–8.5%) in all groups. In nearly 40% of the patients who did initiate CIC following treatment with onabotulinumtoxinA, the duration of CIC was ≤ 6 weeks.

One limitation of this analysis is the small sample size of the subgroups, particularly those who discontinued prior anticholinergic therapy because of side effects, and hence the results, including the low rates of urinary retention, should be interpreted accordingly. In addition, the reasons for discontinuation of prior anticholinergic therapies recorded at study enrolment were patient-reported responses and thus were subjective in nature.

Conclusions

In this pooled analysis of OAB patients with UI who were inadequately managed with anticholinergics, onabotulinumtoxinA 100U provided significant reductions in UI episodes and improvements in all evaluated symptoms of OAB, including urgency, which were reflected in patients' perception of treatment benefit. Similar improvements were observed in subgroups of OAB patients with UI, regardless of the number of prior anticholinergics used or reasons for inadequate management of OAB. OnabotulinumtoxinA was well tolerated, with a safety profile that is consistent with the individual phase 3 trials. The results of this study suggest that onabotulinumtoxinA is an effective and appropriate alternative in OAB patients with UI after failing treatment with one or more anticholinergic.

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Author contributions

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