OnabotulinumtoxinA for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3, Randomized, Placebo Controlled Trial

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Abbreviations and Acronyms

AE = adverse event
CIC = clean intermittent catheterization
HRQOL = health related QOL
I-QOL = Incontinence QOL
ITT = intent to treat
KHQ = King's Health Questionnaire
OAB = overactive bladder
PVR = post-void residual urine volume
QOL = quality of life
TBS = treatment benefit scale
UI = urinary incontinence
UTI = urinary tract infection
UUI = urinary urgency incontinence

Purpose: Overactive bladder affects 12% to 17% of the general population and almost a third experience urinary incontinence, which may severely impact health related quality of life. Oral anticholinergics are the mainstay of pharmacological treatment but they are limited by inadequate efficacy or side effects, leading to a high discontinuation rate. We report the results of the first large (557 patients), phase 3, placebo controlled trial of onabotulinumtoxinA in patients with overactive bladder and urinary incontinence inadequately managed with anticholinergics.

Materials and Methods: Eligible patients with overactive bladder, 3 or more urgency urinary incontinence episodes in 3 days and 8 or more micturitions per day were randomized 1:1 to receive intradetrusor injection of onabotulinumtoxinA 100 U or placebo. Co-primary end points were the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a positive response on the treatment benefit scale at posttreatment week 12. Secondary end points included other overactive bladder symptoms and health related quality of life. Adverse events were assessed.

Results: OnabotulinumtoxinA significantly decreased the daily frequency of urinary incontinence episodes vs placebo (–2.65 vs –0.87, $p < 0.001$) and 22.9% vs 6.5% of patients became completely continent. A larger proportion of onabotulinumtoxinA than placebo treated patients reported a positive response on the treatment benefit scale (60.8% vs 29.2%, $p < 0.001$). All other overactive bladder symptoms improved vs placebo ($p \leq 0.05$). OnabotulinumtoxinA improved patient health related quality of life across multiple measures ($p < 0.001$). Uncomplicated urinary tract infection was the most common adverse event. A 5.4% rate of urinary retention was observed.

Conclusions: OnabotulinumtoxinA 100 U showed significant, clinically relevant improvement in all overactive bladder symptoms and health related quality of life in patients inadequately treated with anticholinergics and was well tolerated.

Key Words: urinary bladder, overactive; urinary incontinence; onabotulinumtoxinA; injections, intramuscular; botulinum toxins

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For another article on a related topic see page 2364.

OVERACTIVE bladder affects 12% to 17% of the general population.[1–3] Approximately a third of individuals with OAB have UUI,[1,2,4,5] which increases in prevalence with advancing age and is more common in women than in men.[1,2,4,6] Currently, anticholinergic agents are the mainstay of pharmacological treatment for OAB. However, they are not always sufficiently effective and have numerous systemic side effects,[7] leading to poor patient compliance and a high discontinuation rate in clinical practice.[8]

OnabotulinumtoxinA delivered directly to the detrusor muscle may represent a new treatment paradigm in patients with OAB and UUI inadequately managed with anticholinergic therapy (inadequate efficacy or intolerable side effects) by treating only the bladder and minimizing the potential for systemic side effects.

In a placebo controlled, dose ranging trial in patients with OAB and UI the 100 U dose of onabotulinumtoxinA provided the appropriate risk-benefit balance.[9] Therefore, we further evaluated the 100 U dose in what we believe to be the first large, multicenter, placebo controlled phase 3 trial.

METHODS

Study

Participants. Patients 18 years old or older with idiopathic OAB who experienced 3 or more urgency UI episodes in a 3-day period and an average of 8 or more micturitions per day were enrolled in the study. Those with a predominance of stress incontinence were excluded. All patients were inadequately treated with prior anticholinergic therapy due to inadequate efficacy or intolerable side effects. Anticholinergic use was not permitted within 7 days of screening or throughout the study. Patients had to have a PVR of 100 ml or less and be willing to perform CIC, if required.

Design. The study was conducted at a total of 72 sites in the United States and Canada (ClinicalTrials.gov NCT00910845) in compliance with Good Clinical Practice regulations. It was approved by the institutional review board at each site and all patients provided written informed consent.

After a screening period of up to 3 weeks, all eligible patients were randomized on day 1 by an interactive voice response system to receive double-blind treatment with onabotulinumtoxinA 100 U (Botox®) reconstituted with 10 ml normal saline or placebo (10 ml normal saline) in a 1:1 ratio, stratified by site and 9 or fewer, or greater than 9 UUI episodes in the 3-day diary. Notably, units of the 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.

Treatment was administered as 20 evenly distributed intradetrusor injections of 0.5 ml per injection site using a flexible or rigid cystoscope and sparing the trigone. Injections were spaced approximately 1 cm apart and the needle was inserted approximately 2 mm into the detrusor. Local anesthesia instillation in the bladder before injection and/or sedation could be used at investigator discretion.

Followup visits occurred at weeks 2, 6 and 12, and every 6 weeks thereafter until study exit at week 24 unless re-treatment was necessary. This could occur from 12 weeks onward if the patient requested it and experienced at least 2 UUI episodes during 3 days. All patients received onabotulinumtoxinA 100 U and posttreatment followup was done according to the first treatment. Therefore, the appropriate period for placebo controlled comparison was up to week 12 because re-treatment was only permitted thereafter. Treatment cycle 1 was defined as the period between the receipt of initial treatment and re-treatment, or study exit when there was no re-treatment.

Efficacy and Safety Evaluations

A 3-day paper bladder diary was used before study visits to collect all OAB symptoms (episodes of urgency, incontinence, micturition and nocturia) and volume per void. Patients recorded their perception of treatment benefit at each posttreatment visit using the TBS,[10] rating their condition as greatly improved, improved, not changed or worsened. The impact of OAB on patient HRQOL was assessed at posttreatment week 12 using 2 validated patient questionnaires, including the I-QOL[11] and KHQ.[12] All HRQOL scores are reported on a scale of 0 to 100 points with higher scores indicating better HRQOL on the I-QOL and the reverse for the KHQ. The predefined, clinically relevant change from baseline in these HRQOL measures or the minimally important difference was an increase of 10 points or more for the I-QOL and a decrease of 5 points or greater for the KHQ.

Co-primary efficacy variables were defined as 1) the change from baseline in the daily average frequency of UI episodes and 2) the proportion of patients with a positive treatment response on the TBS (condition greatly improved or improved) at posttreatment week 12. Secondary efficacy variables were the change from baseline in the daily average frequency of micturition and urgency episodes, the I-QOL total summary score and 2 KHQ multiitem domain scores (role and social limitations). Other efficacy variables were the change from baseline in nocturia episodes, volume voided per micturition and the proportion of patients achieving a 50% or greater, or a 100% reduction in UI episodes. Co-primary, secondary and other efficacy variables were also evaluated at 2 and 6 weeks posttreatment. HRQOL outcomes were evaluated at week 12 posttreatment.

AEs, PVR and CIC were evaluated at posttreatment weeks 2, 6 and 12 or at any other time depending on clinical need. CIC was initiated if PVR was 200 ml or greater, or less than 350 ml with associated symptoms (eg difficult voiding or a sensation of bladder fullness), or PVR was 350 ml or greater regardless of symptoms. The AE of urinary retention was defined as a PVR of 200 ml or greater that required CIC. The AE of UTI was defined as positive urine culture with a bacteriuria count of greater than 10^5 cfu/ml together with leukocyturia greater than 5 per high power field regardless of symptoms.

Statistical Analysis

Efficacy analysis was performed using the ITT population (all randomized patients). Safety analysis was done in the safety population (all patients who received treatment, analyzed by treatment received).

For the co-primary end points of change from baseline in daily UI episodes and TBS responders a sample size of 227 patients per treatment group was expected to provide 82% and 99% power to detect a between group difference, respectively, at a significance level of 0.05. This assumed a mean ± SD between group difference of 2.3 ± 8.5 episodes per day for UI and a 22% between group difference for TBS. Sample size was increased by 15% to account for patient attrition.

For co-primary efficacy outcomes missing values were imputed by last observation carried forward. The daily UI episode variable was analyzed using an ANCOVA model with baseline value and site as covariates, and treatment group as a factor. The TBS variable was analyzed using the Cochran-Mantel-Haenszel chi-square method with the dichotomized number of baseline UUI episodes (9 or fewer, or greater than 9) as a stratification factor. Secondary efficacy outcomes were analyzed using the same ANCOVA model as for UI episodes, except the UUI stratification factor was used rather than the baseline value. The percent change from baseline for OAB symptoms was also calculated.

To account for multiplicity, a hierarchical analysis strategy was used for the primary and secondary end points at week 12. That is, the subsequent parameter could be evaluated for significance only if the first parameter in the ranking order showed statistical significance.[13]

The incidence of AEs and proportion of patients using CIC were evaluated. The change from baseline in PVR was analyzed using the same ANCOVA model as for the secondary efficacy outcomes.

RESULTS

Patient Demographics and Baseline Characteristics

A total of 557 patients were randomized into the study from September 2009 through July 2011, including 280 who received onabotulinumtoxinA 100 U and 277 who received placebo (fig. 1). Baseline characteristics were balanced across treatment groups (table 1). The average duration of OAB was 6.7 years. Patients had used an average of 2.5 anticholinergics for a mean of 2.4 years before study entry. Overall, patients experienced a mean of 5.3

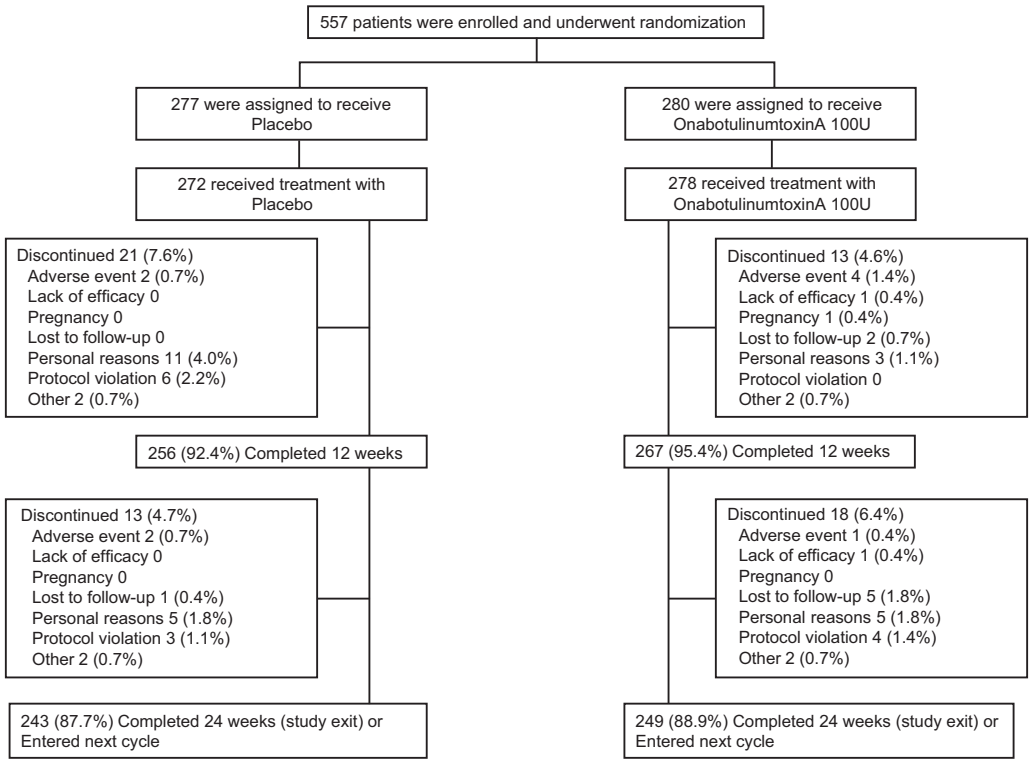

Figure 1. ITT patient population distribution in treatment cycle 1

Table 1. *Baseline demographics and disease characteristics of ITT population*

	Placebo	OnabotulinumtoxinA 100 U
No. pts	277	280
Age (yrs):		
Mean ± SD	61.0 ± 13.1	61.7 ± 12.7
No. 65 or greater (%)	117 (42.2)	121 (43.2)
No. 75 or greater	44 (15.9)	46 (16.4)
No. female (%)	245 (88.4)	252 (90.0)
Mean ± SD OAB duration (yrs)	6.6 ± 7.4	6.8 ± 7.7
Mean ± SD prior anticholinergics:		
Duration (yrs)	2.3 ± 2.5	2.6 ± 3.2
No. anticholinergics	2.5 ± 1.6	2.4 ± 1.6
Mean ± SD No. daily episodes:		
UI	5.1 ± 3.2	5.5 ± 3.6
UUI	4.5 ± 3.1	4.8 ± 3.2
Micturition	11.2 ± 3.1	12.0 ± 4.3
Urgency	7.9 ± 3.7	8.5 ± 4.7
Nocturia	2.0 ± 1.3	2.2 ± 1.5
Mean ± SD vol (ml):		
Voided/micturition	161.1 ± 68.6	156.4 ± 63.2
PVR	25.0 ± 27.0	27.8 ± 30.1
Mean ± SD score:		
Total I-QOL summary	37.3 ± 19.4	36.5 ± 20.6
KHQ role limitations	56.2 ± 30.1	61.2 ± 30.4
KHQ social limitations	39.4 ± 30.1	40.5 ± 30.7

UI episodes per day, of which most were UUI (mean 4.6 episodes per day). Study discontinuation rates were low. In the onabotulinumtoxinA and placebo groups 89% and 88% of patients, respectively, completed the placebo controlled treatment cycle 1 (fig. 1).

Outcomes

Co-primary. At the primary time point of week 12 there were threefold to fourfold greater decreases from baseline in the mean daily frequency of UI episodes for onabotulinumtoxinA 100 U vs placebo (–2.65 vs –0.87, p <0.001, fig. 2, *A*). This corresponded to a mean –47.9% percent reduction from baseline for onabotulinumtoxinA 100 U vs –12.5% for placebo. At week 12, of the patients treated with onabotulinumtoxinA 57.5% achieved a 50% or greater reduction in UI episodes and 22.9% were continent (100% reduction) compared to 28.9% and 6.5%, respectively, of those treated with placebo (p <0.001, fig. 2, *B*). A higher proportion of onabotulinumtoxinA treated patients reported a positive treatment response on the TBS vs those on placebo (60.8% vs 29.2%, p <0.001, fig. 2, *C*). For each co-primary outcome significant between group differences were observed from the first posttreatment evaluation at week 2, which continued through week 12 (each p <0.001).

Secondary and other efficacy. All secondary and other efficacy outcomes were met with large, significant differences between onabotulinumtoxinA and placebo. In patients on onabotulinumtoxinA vs placebo there were decreases from baseline at week 12 in mean micturition (–2.15 vs –0.91, p <0.001), urgency (–2.93 vs –1.21, p <0.001) and nocturia (–0.45 vs –0.24 (p ≤0.05) episodes per day (table 2). Volume voided per micturition was significantly increased for onabotulinumtoxinA vs placebo (41.1 vs 9.7 ml at week 12, p <0.001, table 2). Significant improvements were observed from the first posttreatment evaluation at week 2 for all OAB symptoms that continued through week 12. Importantly, large and clinically relevant differences between onabotulinumtoxinA and placebo were also observed in the percent change from baseline (table 2).

Patient HRQOL at baseline was low, as reflected by I-QOL and KHQ scores in each treatment group (table 1). Large, clinically significant improvements in all I-QOL and KHQ multi-item domain scores were noted after onabotulinumtoxinA vs placebo treatment (each p <0.001, fig. 3). Improvements from baseline for onabotulinumtoxinA were considerably greater than the predefined minimally important differences, in contrast to placebo.

Safety. AEs were primarily localized to the urinary tract (table 3). The most frequently reported AE was UTI, most cases of which occurred in the first 12 weeks (43 of 278 or 15.5% for onabotulinumtoxinA vs 16 of 272 or 5.9% for placebo). All UTIs were uncomplicated with no upper urinary tract involvement. Other notable AEs that occurred in the first 12 weeks at a higher incidence in patients treated with onabotulinumtoxinA were dysuria (34 of 278 or 12.2%) bacteriuria (14 or 5.0%) and urinary retention (15 or 5.4%).

PVR significantly increased in patients treated with onabotulinumtoxinA vs placebo with the highest volume at posttreatment week 2. At weeks 2, 6 and 12 values were 49.5, 42.1 and 32.6 ml in the onabotulinumtoxinA group vs 1.1, 3.1 and 2.5 ml in the placebo group, respectively, p <0.001). Of the 276 patients 24 (8.7%) exhibited a 200 ml or greater increase from baseline in PVR at any time after initial treatment with onabotulinumtoxinA vs none treated with placebo (table 3). The proportion of patients who initiated CIC at any time during treatment cycle 1 was 6.1% (17/278) vs none in the placebo group. For more than half the patients who initiated CIC (10/17), the duration was 6 weeks or less (fig. 4). Interestingly, while all 10 patients with a PVR of 350 ml or greater initiated CIC in accord with protocol guidelines, only 6 of 21 (28.5%) with PVR between 200 and less than 350 ml initiated CIC.

The study discontinuation rate due to AEs was low at 1.8% in the onabotulinumtoxinA group and 1.4% in the placebo group (fig. 1). One death from diverticulitis and pneumothorax, which was unrelated to treatment, was reported in the placebo group during treatment cycle 1 (table 3).

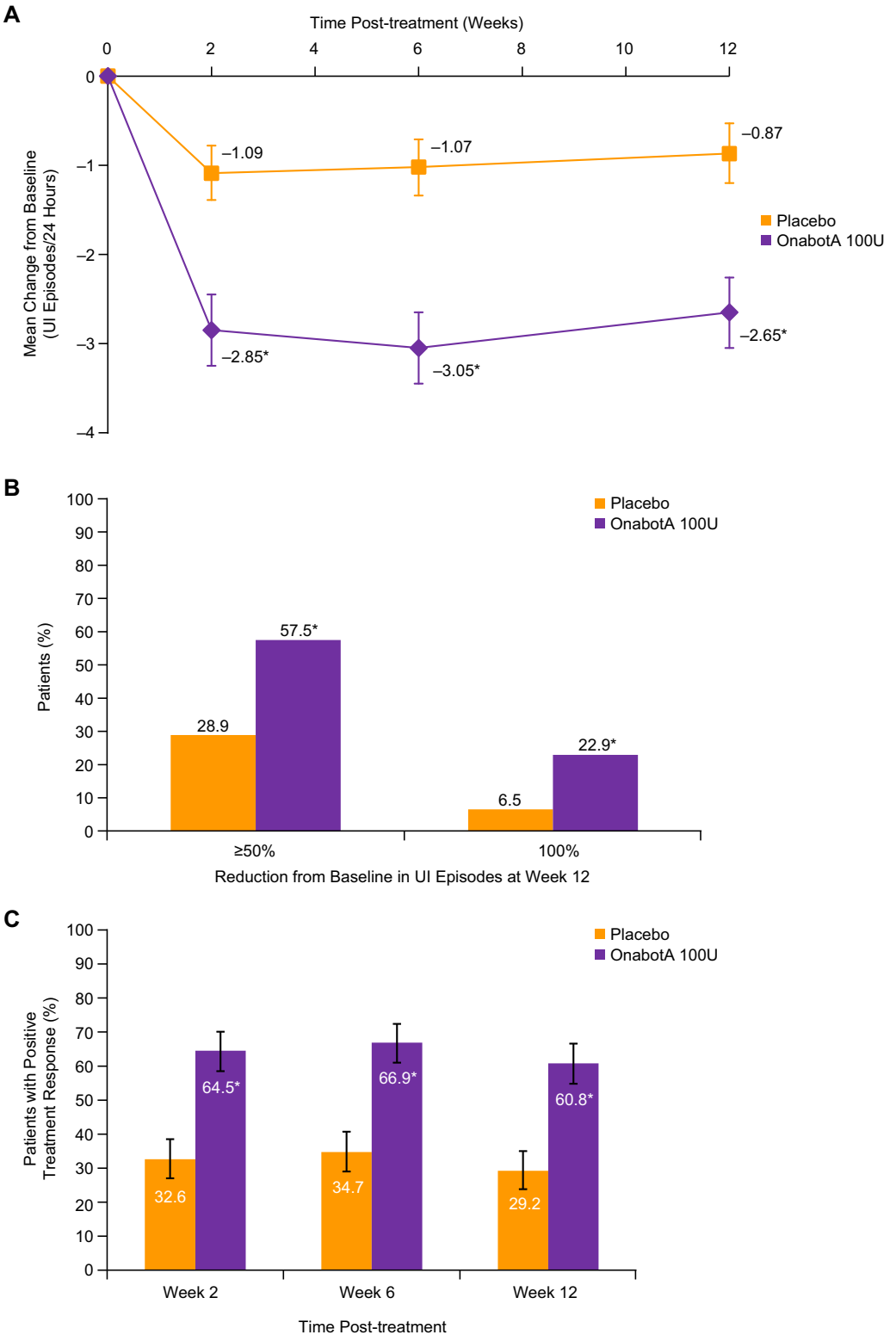

Figure 2. *A*, change from baseline in daily average frequency of UI episodes. *B*, proportion of patients achieving 50% or greater, or 100% decrease from baseline in UI episodes at week 12. *C*, proportion of ITT patient population with positive response (greatly improved or improved condition) on treatment benefit scale. *OnabotA*, onabotulinumtoxinA. Error bars indicate ± 95% CI. Asterisk indicates $p < 0.001$ vs placebo.

Table 2. *Change from baseline in daily average episodes up to posttreatment week 12 in ITT population*

	Mean Change from Baseline (95% CI)		p Value	Mean % Change from Baseline	
	Placebo	100 U OnabotulinumtoxinA		Placebo	100 U OnabotulinumtoxinA
No. pts	277	280		277	280
No. micturition episodes/day:			<0.001		
Wk 2	−0.79 (−1.09, −0.48)	−1.58 (−1.95, −1.21)		5.9	−11.7
Wk 6	−0.98 (−1.28, −0.67)	−1.96 (−2.30, −1.62)		1.1	−15.4
Wk 12	−0.91 (−1.22, −0.59)	−2.15 (−2.50, −1.79)		4.1	−16.9
No. urgency episodes/day:			<0.001		
Wk 2	−1.34 (−1.75, −0.93)	−2.83 (−3.33, −2.32)		−11.5	−28.4
Wk 6	−1.45 (−1.89, −1.02)	−3.21 (−3.69, −2.74)		−13.3	−35.3
Wk 12	−1.21 (−1.67, −0.76)	−2.93 (−3.43, −2.44)		−10.0	−31.6
No. nocturia episodes/day:			≤0.05		
Wk 2	−0.16 (−0.27, −0.05)	−0.40 (−0.54, −0.27)		5.4	−13.0
Wk 6	−0.26 (−0.39, −0.14)	−0.48 (−0.61, −0.35)		1.6	−21.1
Wk 12	−0.24 (−0.37, −0.11)	−0.45 (−0.60, −0.30)		0.2	−20.2
Vol voided/micturition (ml):					
Wk 2	8.1 (1.2, 15.1)	19.7 (12.1, 27.2)	≤0.05	10.0	18.7
Wk 6	9.0 (1.8, 16.1)	32.3 (23.8, 40.9)	<0.001	10.0	30.0
Wk 12	9.7 (2.5, 17.0)	41.1 (30.5, 51.8)	<0.001	10.1	37.3

DISCUSSION

In patients with OAB and UI inadequately managed with anticholinergics onabotulinumtoxinA resulted in significant, clinically relevant reductions in all OAB symptoms. OnabotulinumtoxinA 100 U was consistently effective with a twofold to fourfold im-

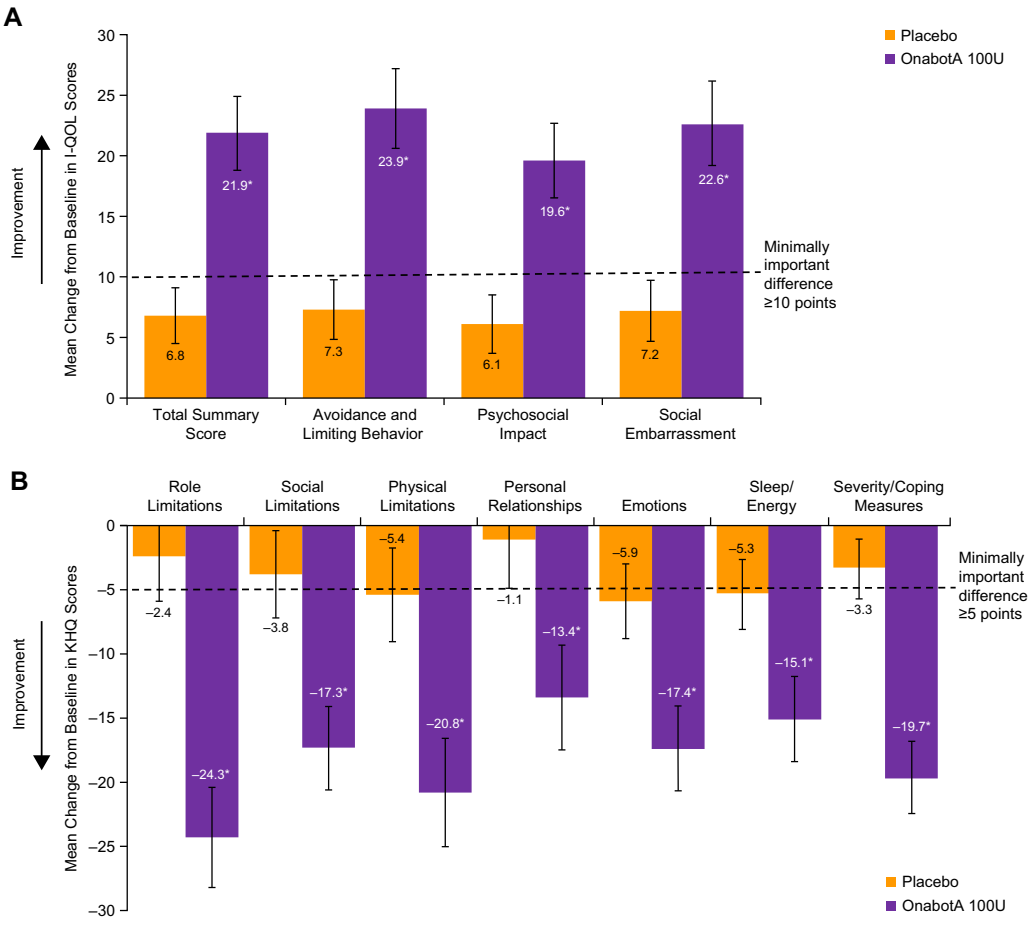

Figure 3. *A*, change from baseline in total I-QOL and domain scores. *B*, 12-week KHQ multi-item domain scores in ITT population. *OnabotA*, onabotulinumtoxinA. Error bars indicate ± 95% CI. Asterisk indicates p <0.001 vs placebo.

Table 3. *Key safety parameters in first 12 weeks after treatment 1 and at any time during treatment cycle 1 in safety population*

	No. First 12 Wks (%)		No. Any Time (%)*	
	Placebo	OnabotulinumtoxinA 100 U	Placebo	OnabotulinumtoxinA 100 U
No. pts	272	278	272	278
AE with 5% or greater incidence:				
UTI†	16 (5.9)	43 (15.5)	25 (9.2)	68 (24.5)
Dysuria	26 (9.6)	34 (12.2)	27 (9.9)	40 (14.4)
Bacteriuria	5 (1.8)	14 (5.0)	10 (3.7)	23 (8.3)
Urinary retention‡	1 (0.4)	15 (5.4)	1 (0.4)	16 (5.8)
Serious AE	8 (2.9)	9 (3.2)	16 (5.9)	18 (6.5)
Death	0	0	1 (0.4)	0
PVR (ml):	0		0	
200 or Greater change from baseline		19 (6.8)		24 (8.7)§
200 or Greater		24 (8.6)		31 (11.2)

* Onset between treatment 1 receipt and re-treatment or study exit.
† Positive urine culture with bacteriuria count greater than 10^5 cfu/ml and leukocyturia greater than 5 per high power field.
‡ PVR 200 ml or greater requiring CIC.
§ In 276 patients due to no baseline value in 2.

provement over placebo in all OAB symptoms. To our knowledge a differential of this magnitude vs placebo has not previously been reported for anticholinergic therapy. The improved ability of the bladder to store urine more effectively was also reflected in the significant increase in volume per void. These results are notable, given that currently there are few pharmacological treatment options for patients who have had an inadequate response to anticholinergics.

OAB can be debilitating for affected patients and may have a profound negative effect on patient HRQOL.[14,15]

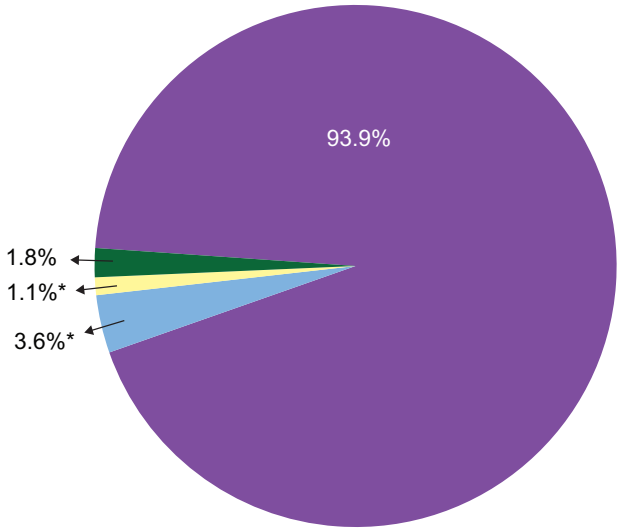

Figure 4. Proportion of safety population with onabotulinumtoxinA 100 U that initiated CIC and posttreatment CIC duration at any time during treatment cycle 1. Asterisk indicates patient who initiated CIC once at week 6 posttreatment for 15 days and at week 12 for 69, and was counted in duration categories 6 weeks or less and greater than 6 to 12 weeks or less. Purple area indicates no CIC. Blue are indicates CIC for 6 or fewer weeks. Yellow area indicates CIC for more than 6 weeks to 12 weeks or less. Green area indicates greater than 12-week CIC.

In this study patients perceived an improvement in their condition after onabotulinumtoxinA treatment with approximately 65% reporting that their condition greatly improved or improved within 2 weeks of treatment. This translated into a positive impact on patient QOL for all HRQOL measures, which showed robust, clinically meaningful improvements.

The ability of onabotulinumtoxinA to synergistically target the afferent and efferent neuronal pathways of bladder control may explain the profound effect observed on all OAB symptoms despite the high level of incontinence in patients at baseline and the failure of prior anticholinergic therapy. OnabotulinumtoxinA directly inhibits efferent acetylcholine mediated detrusor contractions and may inhibit the release of other vesicle mediated neurotransmitters responsible for inappropriate afferent signaling from an overactive bladder.[16] In addition, the over expression of certain receptors in OAB cases may be moderated by onabotulinumtoxinA.[16] Consequently, onabotulinumtoxinA offers a complex inhibitory effect on multiple targets in the bladder wall that may cause OAB.[16–18]

OnabotulinumtoxinA was well tolerated in this study. It was associated with an increase in PVR, which decreased from week 2 through 12, consistent with the transient increase in PVR previously described.[9] At a dose of 100 U 8.7% of patients showed a change from baseline in PVR of greater than 200 ml after treatment, a threshold that is considered clinically relevant. This limited effect on PVR resulted in an acceptable incidence of urinary retention and the need for CIC (6.1%). This is in contrast to previous studies, in which higher doses were frequently used[19,20] or CIC was initiated at PVR thresholds regardless of whether the patient showed associated symptoms.[9] There were no strict criteria

for CIC cessation. As such, the duration of CIC may have been overestimated in our study.

In contrast to urinary retention, the rate of UTI in this study was higher than previously reported in most OAB studies of onabotulinumtoxinA.[21] This may be because we defined UTI conservatively and in a consistent manner across all study sites by the presence of bacteriuria plus leukocyturia irrespective of whether the patient had associated symptoms. All UTI events in treatment cycle 1 were mild to moderate in severity and none were complicated by upper urinary tract involvement.

CONCLUSIONS

Treatment with onabotulinumtoxinA 100 U in patients with OAB and UI who were inadequately managed with anticholinergic therapy resulted in significant, clinically relevant improvements in all OAB symptoms. These improvements were clearly reflected in the patient perception of treatment benefit, including a significant positive impact on HRQOL. A well characterized local safety profile was confirmed. The results of this study suggest that onabotulinumtoxinA is an important new treatment option for patients with OAB and UI who are inadequately managed with anticholinergic therapy.

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APPENDIX

Other EMBARK study group principal investigators: C. Andreou, R.B. Egerdie, D. Eiley, B. Goldfarb, S. Herschorn, J. Mahoney, P.J. Pommerville, S. Radomski and G. Steinhoff, Canada; and P. Aliotta, J.P. Antoci, C.L. Archer-Goode, S.M. Auerbach, T.D. Beam, J.M. Becker, Y. Berger, R.J. Biester, S.D. Blick, R.S. Bradford, D.T. Burzon, K. Cline, R.E. D'Anna, R.R. Dmochowski, M. Efros, J.M. Fialkov, S. Freedman, F. Gaylis, D. Ginsberg, H. Goldman, A. Gousse, I. Grunberger, D.S. Hale, L. Hazan, B.L. Hertzman, T.C. Hlavinka, N.A. Huff, K. Jacoby, M.W. Jalkut, A.R. Johnson, D. Josephson, S. Kalota, J. Kaminetsky, R. Kane, M.M. Kaplan, M. Khorsandi, D. King-Menzner, I.W. Klimberg, C.G. Klutke, K. Krejci, L.S. Kriteman, G.E. Leach, W.W. Leng, D.U. Lipsitz, R.R. Lotenfoe, J. Lumerman, E.J. Margolis, K. Maxwell, C.K. Moore, W. Moseley, S. Mutchnik, R.J. Mynatt, V. Nitti, G. Park, C.K. Payne, J.M. Peters-Gee, P. Pettit, B.J. Roberts, S. Rockove, P.K. Sand, W. Schiff, P. Shenot, P. Siami, S. Siegel, G. Simmons, J. Snyder, D. Sussman, S.E. Sutherland, D.N. Tietjen, E. Torgerson, A. Viselli, M.A. Werner, K. Whitmore, T. Williams, R. Wurzel and E. Zusman, United States.

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