Common Drug Review
Clinical Review Report

July 2015

Drug	onabotulinumtoxinA for injection (Botox)
Indication	For the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.
Listing request	For the treatment of refractory urinary incontinence due to overactive bladder.
Manufacturer	Allergan, Inc.

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ABBREVIATIONS

ANCOVA	analysis of covariance
BSC	best supportive care
CDR	CADTH Common Drug Review
CI	confidence interval
CIC	clean intermittent catheterization
CUAG	Canadian Urological Association Guidelines
EQ-5D	European Quality of Life Five-Dimensions Questionnaire
EQ-VAS	European Quality of Life Visual Analogue Scale
HRQoL	health-related quality of life
iOAB	idiopathic overactive bladder
I-QOL	Incontinence Quality of Life Questionnaire
ITT	intention-to-treat
KHQ	King's Health Questionnaire
LOCF	last observation carried forward
MCID	minimal clinically important difference
MCS	mental component summary
OAB	overactive bladder
Ona A	onabotulinumtoxinA
PP	per-protocol
PCS	physical component summary
PVR	post-void residual
QALY	quality-adjusted life-year
QoL	quality of life
SD	standard deviation
SF-12	Short-Form 12-Item Health Survey
UTI	urinary tract infection

EXECUTIVE SUMMARY

Introduction

Overactive bladder (OAB) is a chronic condition of the lower urinary tract characterized by symptoms of urinary urgency, with or without urge incontinence, and usually with urinary frequency and nocturia. It is estimated that OAB affects 14% to 18% of Canadians. Anticholinergic medications are the mainstay of pharmacological treatment of OAB.

OnabotulinumtoxinA (Ona A) is a purified neurotoxin complex produced from the fermentation of *Clostridium botulinum* type A. Ona A is approved by Health Canada for the treatment of OAB (non-neurogenic) with symptoms of urinary incontinence, urgency, and frequency in adult patients who have an inadequate response to or are intolerant of anticholinergic medication. Mirabegron, sacral neuromodulation, and percutaneous tibial nerve stimulation are possible treatment options for patients who have an inadequate response to or are intolerant of anticholinergic medication.

The indication under review is listed in the following table:

Indication under review
For the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.
Listing criteria requested by sponsor
For the treatment of refractory urinary incontinence due to overactive bladder.

The objective of this review was to evaluate the beneficial and harmful effects of onabotulinumtoxinA injection (Botox) at a dose of 100 units (U) for the treatment of OAB in patients with symptoms of urinary incontinence, urgency, and frequency in adult patients who have an inadequate response to or are intolerant of anticholinergic medications.

Results and Interpretation

Included Studies

Three manufacturer-sponsored studies and one study sponsored by the Assistance publique — Hôpitaux de Paris were included in this review. All studies were randomized, multi-centre, double-blind, placebo-controlled trials comparing Ona A with placebo. Two phase 3 pivotal trials (study 095: n = 557; study 520: n = 548) were of up to 39 weeks' duration with only a 12-week placebo-controlled double-blind phase, and two phase 2 trials (study 077: n = 313; study P030438: n = 99) were of 36-weeks' and six-months' duration, respectively. All studies enrolled patients aged 18 years or older with symptoms of OAB and who were not adequately treated with anticholinergic therapy (inadequate response or intolerance). To be included, patients in studies 095 and 520 had to experience three or more urge-incontinence episodes in a three-day period, while those in study 077 had to experience eight or more urge-incontinence episodes in a one-week period, and those in study P030438 had to experience three or more episodes or urgency with or without urge incontinence in a three-day period. The co-primary efficacy outcomes in studies 095 and 520 were mean change from baseline in the number of incontinence episodes and the proportion of patients with a positive treatment response at week 12, while in study 077 it was mean change from baseline in the number of episodes of weekly urge-

incontinence episodes. In study P030438, it was a > 50% reduction from baseline in both urge incontinence and urgency episodes at three months.

The trials are limited by the lack of an active comparator and their short duration. In addition, there was no clear definition of inadequate response to anticholinergic therapy and it was based on the judgment of the investigators. In the two phase 3 studies, there are no valid placebo-controlled data beyond 12 weeks. The number of patients treated with the Health Canada–approved dose in the phase 2 trials was relatively small and thus these studies are likely underpowered to identify important between-treatment differences for many outcomes of interest.

Efficacy

The two phase 3 pivotal trials reported statistically significantly greater reductions from baseline for Ona A compared with placebo in OAB symptom frequency (incontinence, urge incontinence, micturitions, urgency, and nocturia). While there is no known value for the change or the difference in change of OAB symptom frequency to be judged clinically significant, the clinical expert consulted for this review considered the magnitude of the observed differences between Ona A and placebo at week 12 in the daily frequency of incontinence (1.7 to 1.9 episodes), urge incontinence (1.7 to 2.0 episodes), and urgency (1.5 to 2.4 episodes) to be clinically meaningful. The clinical expert also indicated that the observed differences in the frequency of micturition episodes (1.0 to 1.7) are notable but not a large treatment effect, and that the difference in the frequency of nightly nocturia episodes (≤ 0.3) was not impressive on the whole.

Studies 095 and 520 reported statistically significant and clinically important improvements in disease-specific health-related quality of life measures (King's Health Questionnaire [KHQ] and Incontinence Quality of Life Questionnaire [I-QOL]) for patients treated with Ona A versus placebo. Between-treatment differences in the 12-Item Short-Form Health Survey (SF-12), while statistically significant for the mental component summary (MCS) and utility scores, were of uncertain clinical significance.

The aforementioned study results should be interpreted in the context of the patient populations enrolled in the trials. Specifically, patients had an average frequency of incontinence of approximately 5.1 to 5.7 episodes per day (36 to 40 per week), and an average frequency of urge incontinence of approximately 4.5 to 5.2 episodes per day (32 to 36 per week), which may be higher than the general OAB population with incontinence.

Studies 095 and 520 are limited by the short duration (12 weeks) over which comparative efficacy can be determined. Studies 077 and P030438 provide longer-term comparative data (36 weeks and six months, respectively); however, Ona A did not demonstrate statistically significant improvements compared with placebo for many OAB symptoms at these time points. All four of the reviewed studies are limited to comparative efficacy (versus placebo) for a single treatment.

Patients completing either of two phase 3 pivotal trials (study 095 or 520) were eligible to be enrolled in an open-label extension study. The review of long-term efficacy and safety data from this open-label extension trial has several limitations: the open-label, non-comparative design of the extension trial; the repeated, cyclical administration of treatment in the extension trial, which was not a design feature of the phase 3 trials, which were limited to a single dose of treatment; and the non-availability of the most current data for the extension trial. Bearing in mind these limitations, the extension trial efficacy data seem generally supportive of the phase 3 trial findings.

Harms

There were no deaths during the double-blind phase in studies 095 and 520, but three deaths (two in the placebo group and one in the Ona A group) were reported in the open-label extension phase of the included trials; however, none of these deaths were considered related to study treatment.

The proportion of patients who experienced adverse events, serious adverse events, and withdrawals due to adverse events was higher in the Ona A groups. Overall, the most frequent adverse events associated with Ona A were urinary tract infection (UTI), dysuria, urinary retention, bacteriuria, and increased residual urine volume. The clinical expert consulted for this review indicated that the higher incidence of UTI in the Ona A groups is likely due to the higher frequency of urinary retention observed among Ona A–treated patients, which would predispose them to infection. Further, the higher incidence of urinary retention in the Ona A groups likely explained the higher incidence of clean intermittent catheterization (CIC) in the Ona A groups. The Health Canada–approved product monograph states that Ona A is contraindicated in patients with OAB who are not willing and able to have CIC initiated. No increased risk of cardiac events, anaphylaxis, or hypersensitivity reactions was observed for Ona A compared with placebo. Limited data on adverse events were reported for the P030438 study.

Bearing in mind the limitations of the open-label extension study mentioned earlier, there do not appear to be any new safety signals from the extension trial data.

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis of Ona A plus best supportive care (BSC) (which consisted of incontinence pads and treatment for adverse events such as skin and UTIs), compared with BSC alone, for the treatment of refractory urinary incontinence in adult patients with OAB.[1] The analysis was based on a Markov model with five health states based on average number of daily urinary-incontinence episodes and a relative reduction in the average number of daily urinary-incontinence episodes from baseline, and one absorbing state (death). Efficacy and transition probabilities were derived from the patient-level data from the pooled study data set of two phase 3 trials (191622-520 and 191622-095) and an extension trial (191622-096). The median time to qualify for re-treatment was estimated at 34.10 weeks (approximately eight months) based on an analysis of the ongoing long-term extension study data (study 096). The proportion of patients receiving sacral nerve stimulation was estimated based on physician surveys. Modelled adverse events included catheterization (duration and frequency of use) and UTI. The manufacturer captured treatment costs associated with Ona A and BSC, as well as costs of medical resource utilization. Utility values for each health state were obtained by mapping quality of life data captured in the clinical trials to the European Quality Of Life Five Dimensions Questionnaire (EQ-5D) utility instrument. The time horizon for the analysis was set at five years with a cycle length of 12 weeks (i.e., three months).

Results of Manufacturer's Analysis

The manufacturer reports that the incremental cost per quality-adjusted life-year (QALY) for Ona A plus BSC was $34,029 compared with BSC alone.

Interpretations and Key Limitations

A key limitation was the manufacturer's modelling of health state utilities. Other limitations included the stopping rule for Ona A, proportion of patients receiving sacral nerve stimulation, time to initiation of sacral nerve stimulation, and efficacy of anticholinergics in the BSC group compared with real-life clinical practice. When accounting for these limitations, the CADTH Common Drug Review (CDR) found the incremental cost-utility ratio of Ona A plus BSC compared with BSC alone ranged from $56,932 to

$60,451 per QALY gained, with a most likely incremental cost-utility ratio estimate of $59,388 per QALY gained. The place in therapy and cost-effectiveness of Ona A compared with mirabegron is unclear at this time.

Conclusions

Two phase 3 and two phase 2 placebo-controlled studies compared Ona A with placebo in adult patients with symptoms of idiopathic overactive bladder that had not been adequately managed with anticholinergic therapies. In the phase 3 studies (095 and 520), compared with placebo, Ona A resulted in statistically significantly greater reductions from baseline in incontinence episodes, urge-incontinence episodes, urgency episodes, micturitions, and nocturia episodes. There is no generally recognized standard for the change or the difference in change for these outcomes to be judged clinically significant. However, the clinical expert consulted for this review considered the observed differences to be of clinical importance. In addition, studies 095 and 520 reported statistically significant and clinically important improvements in disease-specific health-related quality of life measures (KHQ and I-QOL) for patients treated with Ona A versus placebo. In the phase 2 studies (077 and P030438), there was no statistically significant difference between Ona A and placebo in terms of urge incontinence frequency.

The proportion of patients who experienced adverse events, serious adverse events, and withdrawals due to adverse events was higher in the Ona A groups. Overall, the most frequent adverse events associated with Ona A were UTI, dysuria, urinary retention, bacteriuria, increased residual urine volume, and use of CIC for urinary retention. No increased risk of cardiac events or anaphylaxis or hypersensitivity reactions was observed for Ona A compared with placebo.

The trials, which assessed only a single dose, are limited by the lack of an active comparator and their short duration.

TABLE 1: SUMMARY OF RESULTS

Outcome	Study 191622–095[a]		Study 191622-520[a]		Study 191622–077[b]		Study P030438[c]	
	Ona A 100 U (N = 280)	Placebo (N = 277)	Ona A 100 U (N = 277)	Placebo (N = 270)	Ona A 100 U (N = 54)	Placebo (N = 44)	Ona A 100 U (N = 22)	Placebo (N = 29)
Mean frequency of micturition episodes								
Baseline, mean (SD)	11.98 (4.3)	11.20 (3.1)	12.01 (4.0)	11.77 (3.6)	80.3 (22.6)	73.3 (23.0)	NR	NR
Change from baseline, mean (95% CI)	−2.0 (−2.4 to −1.6)	−1.0 (−1.3 to −0.6)	−2.4 (−2.7 to −2.0)	−0.6 (−1.0 to −0.2)	−21.7 (19.8)	−8.3 (22.9)	NR	NR
MD (95% CI), *P* value versus placebo	−1.0 (−1.5 to −0.6) *P* < 0.001	ref	−1.7 (−2.2 to −1.3) *P* < 0.001	ref	−8.2 (−16.5 to 0.12) *P* = 0.053	ref	*P* < 0.001	ref
Mean frequency of incontinence episodes								
Baseline, mean (SD)	5.47 (3.6)	5.09 (3.2)	5.52 (3.8)	5.70 (3.9)	NR	NR	NR	NR
Change from baseline, mean (95% CI)	−2.5 (−2.9 to −2.1)	−0.9 (−1.3 to −0.5)	−3.0 (−3.4 to−2.5)	−1.1 (−1.5 to −0.6)	NR	NR	NR	NR
MD (95% CI), *P* value versus placebo	−1.7 (−2.1 to −1.2) *P* < 0.001	ref	−1.9 (−2.4 to−1.4) *P* < 0.001	ref	NR	NR	NR	NR
Mean daily frequency of urge-incontinence episodes								
Baseline, mean (SD)	4.8 (3.2)	4.5 (3.1)	5.1 (3.7)	5.2 (3.7)	27.8 (22.7)	32.5 (20.2)	NR	NR
Change from baseline, mean (95% CI)	−2.4 (−2.8 to −2.0)	−0.7 (−1.1 to −0.3)	−2.8 (−3.4 to −2.4)	−0.9 (−2.1 to −0.7)	−18.4 (20.2)	−17.4 (18.2)	NR	NR
MD (95% CI), *P* value versus placebo	−1.7 (−2.1 to −1.2) *P* < 0.001	ref	−2.0 (−2.5 to −1.5) *P* < 0.001	ref	−4.8 (−10.4 to 0.8) *P* = 0.094	ref	NR	NR
Percentage of patients with ≥ 50% reduction in urge-incontinence episodes	61.2%	29.1%	64.8%	31.5%	70.4%	52.3%	65%	29%
Percentage of patients with ≥ 75% reduction in urge-incontinence episodes	48.3%	15.5%	48.1%	20.8%	55.6%	36.4%	40%	18%
Percentage of patients with 100% reduction in urge-incontinence episodes	28.9%	7.8%	31.8%	13.1%	37.0%	15.9%	NR	NR

Outcome	Study 191622–095[a]		Study 191622-520[a]		Study 191622–077[b]		Study P030438[c]	
	Ona A 100 U (N = 280)	Placebo (N = 277)	Ona A 100 U (N = 277)	Placebo (N = 270)	Ona A 100 U (N = 54)	Placebo (N = 44)	Ona A 100 U (N = 22)	Placebo (N = 29)
Mean frequency of nocturia episodes								
Baseline, mean (SD)	2.15 (1.5)	2.01 (1.3)	2.19 (1.5)	2.08 (1.5)	13.9 (6.9)	12.3 (8.2)	NR	NR
Change from baseline, mean (95% CI)	−0.5 (−0.6 to −0.3)	−0.3 (−0.4 to −0.1)	−0.5 (−0.7 to −0.3)	−0.2 (−0.6 to 0.05)	−4.1 (SD 7.0)	−0.3 (SD 6.8)	NR	NR
MD (95% CI), *P* value versus placebo	−0.2 (−0.4 to −0.02) *P* = 0.029	ref	−0.3 (−0.5 to −0.08) *P* = 0.007	ref	−2.1 (−5.0 to 0.9) *P* = 0.166	ref	NR	NR
Mean frequency of urgency episodes								
Baseline, mean (SD)	8.54 (4.7)	7.85 (3.7)	9.11 (4.6)	8.78 (4.5)	69.9 (28.2)	62.0 (26.6)	NR	NR
Change from baseline, mean (95% CI)	−2.8 (−3.3 to −2.2)	−1.3 (−1.8 to −0.7)	−3.4 (−3.9 to −2.8)	−1.0 (−1.5 to −0.4)	−30.5 (SD 27.6)	−14.1 (SD 30.2)	NR	NR
MD (95% CI), *P* value versus placebo	−1.5 (−2.2 to −0.9) *P* < 0.001[d]	ref	−2.4 (−3.1 to −1.8) *P* < 0.001[d]	ref	−11.7 (−23.0 to −0.4) *P* = 0.043	ref	NS	ref
Time to request re-treatment and proportion of patients who requested re-treatment								
Patients who requested re-treatment, n (%)	173 (61.8)	223 (80.5)	175 (63.2)	229 (84.5)	NA	NA	NA	NA
Time to request re-treatment, median weeks (95% CI)	21.1 (18.3 to 24.0)	12.4 (12.3 to 13.0)	18.1 (17.4 to 22.9)	12.9 (12.4 to 13.1)	NA	NA	NA	NA
P value versus placebo	*P* < 0.001	ref	*P* < 0.001	ref	NA	NA	NA	NA
HRQoL outcomes								
KHQ role limitations: MD (95% CI), *P* value versus placebo at week 12	−20.6 (−25.6, −15.7). *P* < 0.001	ref	−19.8 (−24.8, −14.7). *P* < 0.001	ref	NA	NA	NA	NA
KHQ social limitations: MD (95% CI), *P* value versus placebo at week 12	−13.9 (−18.1, −9.7). *P* < 0.001	ref	−13.2 (−17.8, −8.6). *P* < 0.001	ref	NA	NA	NA	NA
KHQ symptoms component: MD (95% CI), *P* value versus placebo at week 12	NA	NA	NA	NA	−9.0 (−15.8, −2.3). *P* = 0.009	ref	NA	NA

Outcome	Study 191622–095[a]		Study 191622-520[a]		Study 191622–077[b]		Study P030438[c]	
	Ona A 100 U (N = 280)	Placebo (N = 277)	Ona A 100 U (N = 277)	Placebo (N = 270)	Ona A 100 U (N = 54)	Placebo (N = 44)	Ona A 100 U (N = 22)	Placebo (N = 29)
I-QOL total summary score: MD (95% CI), *P* value versus placebo at week 12	14.9 (11.1, 18.7). *P* < 0.001	ref	16.9 (13.2, 20.6). *P* < 0.001	ref	14.8 (5.3, 24.4). *P* = 0.002	ref	0.01 ≤ *P* < 0.05	ref
Harms								
N	278	272	274	270	55	43	22	29
Patients with at least one AE, n (%)	171 (61.5)	144 (52.9)	142 (51.8)	92 (34.1)	44 (80.0)	33 (76.7)		
Patients with at least one SAE, n (%)	9 (3.2)	8 (2.9)	13 (4.7)	10 (3.7)	5 (9.1)	5 (11.6)	NR	NR
WDAEs, n (%)	4 (1.4)	2 (0.7)	2 (0.7)	1 (0.4)	0 (0.0)	1 (2.3)	NR	NR
Deaths, n (%)	0	0	0	0	0	0		
AEs of special interest								
Anaphylaxis/ hypersensitivity reactions	0 (0.0)	1 (0.4)	0	1 (0.4)	0	0	NR	NR
Use of CIC for urinary retention	17 (6.1)[e]	0[e]	19 (6.9)[e]	2 (0.7)[e]	6 (10.9)	1 (2.3)	1 (4.5)	1 (3.4)
UTI	43 (15.5)	16 (5.9)	56 (20.4)	14 (5.2)	20 (36.4)	7 (16.3)	0[f]	2 (8.7)[f]
Cardiac events	1 (0.4)	2 (0.7)	3 (1.1)	1 (0.4)	3 (5.5)	1 (2.3)		

AE = adverse event; CI = confidence interval; CIC = clean intermittent catheterization; HRQoL = health-related quality of life; I-QOL = Incontinence Quality of Life Questionnaire; KHQ = King's Health Questionnaire; MD = mean difference; NA = not applicable; NR = not reported; NS = not statistically significant; Ona A = onabotulinumtoxinA; ref = reference group; SAE = serious adverse event; SD = standard deviation; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] Daily frequency at week 12. *P* values for between-treatment comparisons are from an analysis of covariance model with treatment group as a factor, baseline outcome value, and site as covariates.

[b] Weekly frequency at week 12. *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline outcome value as covariates.

[c] Daily frequency at 90 days.

[d] *P* value is from stratified log-rank test with baseline urinary urge-incontinence episodes as stratification factor.

[e] During treatment cycle 1.

[f] At month 6.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Overactive bladder (OAB) is a chronic condition of the lower urinary tract defined by the International Continence Society as a syndrome experienced during the storage phase of the bladder. It is characterized by symptoms of urinary urgency, with or without urge incontinence, usually with increased daytime frequency and nocturia in the absence of other obvious pathology.[2-5]

It is estimated that OAB affects 14% to 18% of Canadians.[6-8] OAB symptom prevalence tends to increase with age (12.2% for < 60 years old versus 23.8% for > 60 years old).[8] Similar OAB prevalence among men and women has been reported in some studies; however, OAB with urge incontinence is more frequently reported in women than men (7.1% versus 3.3%).[8] A true incidence measure of OAB is difficult as many patients are embarrassed to discuss their symptoms with their physician or feel that OAB is a normal part of aging and must be accepted.[9,10] OAB is therefore a condition that often remains underdiagnosed.[10]

OAB may affect an individual's psychological and social well-being by leaving sufferers feeling anxious, frustrated, and embarrassed.[9] OAB has been linked to higher levels of depression, higher levels of work impairment (e.g., absenteeism, presenteeism, decreased productivity), and greater rates of unemployment.[11] Even mild symptoms of urinary incontinence have the potential to affect patient quality of life by having a negative impact on everyday participation in a variety of interpersonal, professional, and social activities.[9]

1.2 Standards of Therapy

According to the Canadian Urological Association Guidelines (CUAG),[6] it is recommended that behavioural and lifestyle modification be implemented first for the treatment of urinary incontinence. Pharmacological therapies are also used in OAB patients who do not achieve symptom relief with conservative management. Anticholinergic drugs are commonly used in OAB patients; treatment options include darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium.[6] A recent systematic review and meta-analysis showed that these medications had comparable benefits and tolerability, with clinically minor differences between drugs.[12] The main safety concerns with these drugs include anticholinergic adverse effects, such as dry mouth, dizziness, blurred vision, constipation, urinary retention, cognitive disorders, confusion, and drowsiness. Anticholinergic drugs are contraindicated in patients with uncontrolled narrow-angle glaucoma, gastric retention, and those at risk for urinary retention. Canadian guidelines state that the choice of anticholinergic agent may depend on physician experience and preference, formulary coverage, patient preference, and insurance coverage.[6] Mirabegron, a selective beta 3 agonist recently approved by Health Canada, may be an alternative for patients who have contraindications to or are intolerant of anticholinergic medications. It is estimated that three-quarters of patients will be successfully treated with behavioural and/or drug therapy.[13]

According to the American Urological Association and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction guidelines,[14] pharmacological therapies, including oral beta 3 agonist or anticholinergic, should be offered as second-line therapy to patients with non-neurogenic OAB who are unable or unwilling to comply with behavioural therapy.

According to CUAG, patients who have failed two or more adequate treatments of anticholinergic drugs are considered to have refractory urge incontinence.[6]

Sacral neuromodulation and percutaneous tibial nerve stimulation are treatment options for refractory urge incontinence, with a response rate that ranges from 39% to 81%; however, these therapies are expensive and not widely available or accessible.[6]

1.3 Drug

OnabotulinumtoxinA (Ona A) is a purified neurotoxin complex produced from the fermentation of *Clostridium botulinum* type A. [15] This CADTH Common Drug Review (CDR) submission is specific to the approved Health Canada indication for the treatment of (non-neurogenic) OAB with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.[15] The recommended dose is 100 U, administered via injections into the detrusor muscle across 20 sites of the bladder. Patients may be considered for re-treatment no sooner than three months after prior bladder injection, when the clinical effect of the previous injection diminishes.[15] Ona A affects the efferent pathways of detrusor activity by inhibiting the release of acetylcholine following intradetrusor injections.

Indication under review
For the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.
Listing criteria requested by sponsor
For the treatment of refractory urinary incontinence due to overactive bladder.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of Ona A injection (Botox) for the treatment of OAB in patients with symptoms of urinary incontinence, urgency, and frequency in adult patients who have an inadequate response to or are intolerant of anticholinergic medications.

2.2 Methods

Studies selected for the systematic review included pivotal trials submitted by the manufacturer in support of the Health Canada indication for which the submission was made (OAB), in addition to trials meeting the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with overactive bladder with symptoms of urinary incontinence, urgency, and frequency who have an inadequate response to or are intolerant of anticholinergic medications **Subgroups of interest** Age (< 65 years vs. ≥ 65 years)
Intervention	Ona A injection (Botox) at doses of 100 U
Comparators	• mirabegron • anticholinergics (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium) • placebo
Outcomes	**Key efficacy outcomes** Bladder activity: • micturition episodes • urinary-incontinence episodes • urinary urge-incontinence episodes • nocturia episodes • urgency episodes • time to request of re-treatment and proportion of patients who requested re-treatment Quality of life: • any validated HRQoL measure (generic or condition-specific instruments) **Harms outcomes** Mortality, AEs, SAEs, WDAEs, AEs of special interest (e.g., anaphylaxis or hypersensitivity reactions, use of CIC for urinary retention, urinary tract infection, cardiac events)
Study Design	Published and unpublished DB RCTs ≥ 12 weeks in duration

AE = adverse event; CIC = clean intermittent catheterization; DB = double-blind; HRQoL = health-related quality of life; Ona A = onabotulinumtoxinA; RCT = randomized controlled trial; SAE = serious adverse event; vs = versus; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Botox (onabotulinumtoxinA) and overactive bladder.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on April 29, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on October 15, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

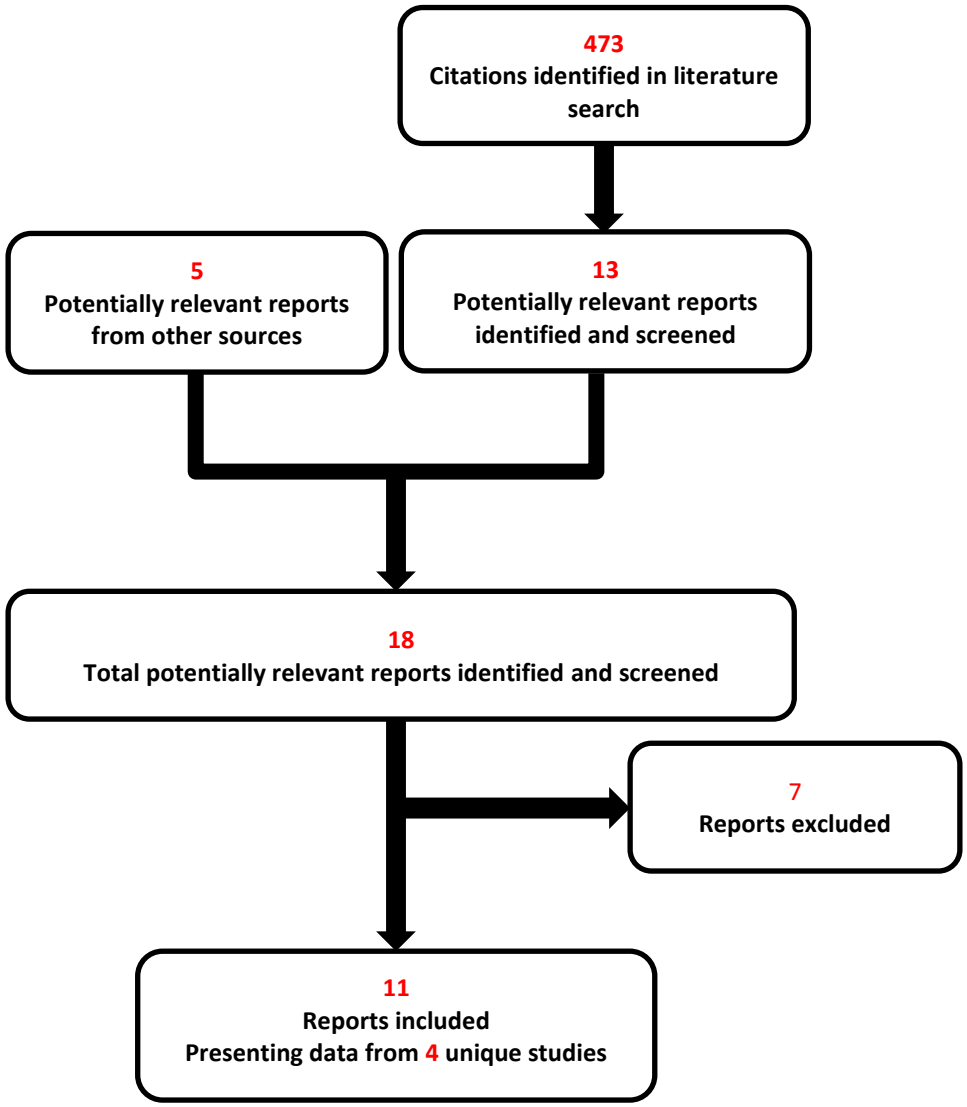
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of 473 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 3: DETAILS OF INCLUDED STUDIES

		191622-095	191622-520	191622-077	P030438
DESIGNS & POPULATIONS	**Study Design**	DB, multi-centre RCT		DB, multi-centre RCT	DB, multi-centre RCT
	Locations	US, Canada	Europe, US	Europe, US, Canada	France
	Randomized (N)	557	548	313	99
	Inclusion Criteria	Adults (≥ 18 years) with iOAB symptoms ≥ 6 mo (≥ 3 urge-incontinence episodes in a three-day period based on a pre-baseline diary) with ≥ 8 micturitions/day who had not been adequately treated with prior anticholinergic therapy due to inadequate efficacy or intolerable side effects and who were willing to use CIC to empty the bladder and had a PVR urine volume ≤ 100 mL		Adults (≥ 18 years) with iOAB symptoms ≥ 6 mo (≥ 8 urge-incontinence episodes in a 1-week period based on a pre-baseline diary) with ≥ 8 micturitions/day who had not been adequately treated with prior anticholinergic therapy due to inadequate response or intolerable side effects	Adults (≥ 18 years) with iOAB symptoms > 6 mo (≥ 3 urgency with or without urge incontinence in a three-day period based on a pre-baseline diary) with ≥ 8 micturitions/day and ≥ 3 urgency episodes/day, a proven DO and who were refractory or had contraindications to (or discontinued) anticholinergics because of adverse events Patients had used anticholinergics for a minimum 3 mo and maximum 12 mo before inclusion Patients willing to use CIC
	Exclusion Criteria	A predominance of stress incontinence; previous use of botulinum toxin for any urologic condition; symptoms of OAB for any known neurologic reason; any disease that may affect bladder function; any pelvic or urologic abnormalities; bladder surgery; patients who received anticholinergic within 7 days of screening or throughout the study; patients treated for two or more UTIs within 6 mo; patients who use CIC		A predominance of stress incontinence; previous use of botulinum toxin for any condition; symptoms of OAB for any known neurologic reason; any disease that may affect bladder function; any pelvic or urologic abnormalities; had PVR urine volume > 200 mL at screening or 24-hour total urine volume voided greater than 3,000 mL; treated for two or more UTIs within 6 mo; patients who use CIC	Symptomatic UTI; a predominance of stress incontinence, PVR > 150 mL; 24-hour total urine volume voided greater than 3,000 mL; urinary flow rate < 15 mL/s; allergy or contraindication to study medication; previous use of botulinum toxin type A in the past 3 mo; ongoing anticoagulant or antineoplastic treatment
DRUGS	**Intervention**	100 U onabotulinumtoxinA, as 20 evenly distributed intradetrusor injections of 0.5 mL per injection		50, 100, 150, 200, or 300 U onabotulinumtoxinA, as 20 evenly distributed	50, 100, 150 U onabotulinumtoxinA, as 15 homogeneously distributed injections in the detrusor

		191622-095	191622-520	191622-077	P030438
				intradetrusor injections of 0.5 mL per injection	
	Comparator(s)	Placebo administered in manner similar to the intervention		Placebo administered in manner similar to the intervention	Placebo administered in manner similar to the intervention
	Phase	**3**		**2**	**2**
	Double-blind	12 weeks		36 weeks	6 mo
	Follow-up	At least 12 weeks (after DB phase) and up to 27 weeks (after DB phase) for patients receiving a second treatment		36 weeks (0 weeks after DB phase)	6 mo (0 weeks after DB phase)
OUTCOMES	**Primary End Point**	Co-primary at week 12: • Change from baseline in the frequency of daily incontinence episodes • Percentage of patients with a positive treatment response on the TBS		change from baseline in frequency of urge-incontinence episodes at week 12	Proportion of patients with > 50% reduction from baseline in both urge incontinence and urgency episodes at 3 mo
	Other End Points	• Micturition episodes • Nocturia episodes • Urgency episodes • Time to request re-treatment • HRQoL (I-QOL, KHQ) • Harms		• Micturition episodes • Nocturia episodes • Urgency episodes • HRQoL (I-QOL, KHQ) • Harms	• Micturition episodes • Urgency episodes • HRQoL (I-QOL) • Harms
NOTES	**Publications**	Nitti et al.[16]	Chapple et al.[17]	Dmochowski et al.[18]	Denys et al.[19]

DB = double-blind; CDR = CADTH Common Drug Review; CIC = clean intermittent catheterization; DO = detrusor overactivity; HRQoL = health-related quality of life; iOAB = idiopathic overactive bladder; I-QOL = Incontinence Quality of Life Questionnaire; KHQ = King's Health Questionnaire; mo = months; PVR = post-void residual; RCT = randomized controlled trial; s = second; TBS = treatment benefit scale.

Note: Four additional reports (manufacturer's submission binder,[23] Health Canada reviewer's report,[24] Rovner et al.,[25] Fowler et al.[26]) were used in the CDR review.

Source: Study 191622-520 Clinical Study Report,[20] Study 191622-095 Clinical Study Report,[21] Study 191622-077 Clinical Study Report,[22] Chapple et al.,[17] Nitti et al.,[16] Dmochowski et al.,[18] Denys et al.[19]

3.2 Included Studies

3.2.1 Description of Studies

Four randomized controlled trials met the criteria for inclusion in this systematic review: three were manufacturer-sponsored, and one study was sponsored by the Assistance publique — Hôpitaux de Paris. All included studies were multi-centre, randomized, double-blind, placebo-controlled trials comparing Ona A with placebo. Study 191622-095 (referred to as study 095) and study 191622-520 (referred to as study 520) were phase 3 trials, while study 191622-077 (referred to as study 077) and study P030438 were phase 2 trials. All trials investigated the efficacy and safety of Ona A for the treatment of idiopathic overactive bladder (iOAB) in patients who had not been adequately treated with anticholinergic therapy (inadequate efficacy or intolerance) and were 18 years of age or older.

The phase 3 trials (study 095, n = 557; and study 520, n = 548) were of identical study design.[16,17,20,21] Patients were randomized in a 1:1 ratio to receive Ona A 100 U, or placebo; randomization was stratified by centre and number of incontinence episodes reported at baseline (≤ 9 or > 9 episodes, over the three-day diary). Ona A or placebo was administered as 20 evenly distributed intradetrusor injections of 0.5 mL per injection site. The co-primary efficacy outcomes were change from baseline in the daily episodes of incontinence, and the proportions of patients with a positive treatment response on the treatment benefit scale. The double-blind phase of the two studies was 12 weeks; the minimum study duration was 24 weeks, with a maximum duration of 39 weeks. Patients who received only one treatment were evaluated at week two, six, 12, 18, and 24. After week 12, all patients who were eligible for a second treatment received Ona A 100 U; hence, the appropriate period for placebo-controlled comparison was up to week 12, with treatment cycle 1 defined as the period between the receipt of first treatment and re-treatment, or study exit when there was no re-treatment. Data presented in the systematic review are from the 12-week double-blind treatment phase from each trial. Patients completing either of two phase 3 trials were eligible to be enrolled in an open-label extension study (study 191622-096). Data from this open-label extension study are summarized in APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY.

The phase 2 trials (study 077: n = 313; study P030438: n = 99) were of a 36-week and six-month duration, respectively.[18,19,22] Patients in study 077 were randomized in a 1:1:1:1:1:1 ratio to receive Ona A 50 U, 100 U, 150 U, 200 U, or 300 U, or placebo. Ona A or placebo was administered as 20 evenly distributed intradetrusor injections of 0.5 mL per injection site. Patients were evaluated at week one, two, six, 12, 18, 24, and 36, with primary end point at week 12. The primary efficacy outcome was change from baseline in the number of weekly episodes of urge incontinence. Patients in study P030438 were randomized in a 1:1:1:1 ratio to receive Ona A 50 U, 100 U, or 150 U, or placebo; randomization was stratified by centre. Ona A or placebo was administered as 15 homogeneously distributed injections in the detrusor. Patients were evaluated at day eight and months one, three, five, and six with primary end point at week 12 (month three). The primary efficacy outcome was proportion of patients with a greater than 50% reduction from baseline of both urge incontinence and urgency episodes at three months. Because Ona A 100 U is the Health Canada–approved dose for the treatment of OAB, only data for this dose are included in the current report from studies 077 and P030438.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Studies 095 and 520 enrolled patients aged 18 years or older with symptoms of iOAB and who had experienced three or more urge-incontinence episodes in a three-day period (three-day patient bladder diary completed during the screening period) and who were not adequately managed with anticholinergic therapy (defined as inadequate response after at least four weeks of anticholinergic therapy or limiting side effects after at least a two-week period). Study 077 enrolled patients aged 18 years or older with symptoms of iOAB and who had experienced eight or more urge-incontinence episodes in a one-week period (based on patient bladder diary entries collected over seven consecutive days during the screening period), and who had inadequate response or intolerable adverse effects after at least one month of anticholinergics therapy. Study P030438 enrolled patients aged 18 years or older with symptoms of iOAB with three or more episodes of urgency with or without urge incontinence in a three-day period (based on a three-day micturition diary completed during the screening period) and who were refractory or had contraindications to anticholinergics, or who discontinued anticholinergics because of adverse events. Patients had to have used anticholinergics for at least three months, but not more than 12 months before inclusion.

Patients were excluded if they had used anticholinergics or any other medications or therapies to treat symptoms of OAB within seven days of the start of the screening period for studies 095 and 520, and within 21 days of randomization for study 077. However, in study P030438, a stable regimen of anticholinergics was maintained during the study period in patients already using anticholinergics. Patients who had a history of two or more urinary tract infections (UTIs) within six months of randomization were excluded from studies 095, 520, and 077, while patients with symptomatic UTI were excluded from study P030438. Patients were excluded from studies 095 and 520 if they had a post-void residual (PVR) of more than 100 mL, while those with PVR > 150 mL were excluded from study P030438, and those with PVR > 200 mL were excluded from study 077. Patients with predominance of stress incontinence were excluded from all four studies, and patients who used clean intermittent catheterization (CIC) or an indwelling catheter to manage their urinary incontinence, or had any pelvic or urological abnormalities, or bladder surgery or disease other than OAB, were excluded from studies 095, 520, and 077.

b) Baseline Characteristics

Baseline characteristics were similar across treatment groups within studies (Table 4). The mean age per treatment group ranged from 58.7 to 62.5 years, and the percentage of females ranged from 82% to 93%.

In the two phase 3 trials, the majority were Caucasian. The mean duration of OAB ranged from 6.6 to 6.8 years in study 095, and from 5.2 to 5.7 years in study 520. The mean daily frequency of incontinence episodes at baseline ranged from 5.1 to 5.5 in study 095, and from 5.5 to 5.7 in study 520. The mean daily frequency of micturition episodes at baseline ranged from 11.2 to 12.0 in study 095, and from 11.8 to 12.0 in study 520 (Table 4). Mean number of prior anticholinergic medications used ranged from 2.4 to 2.5 in study 095, and from 2.3 to 2.5 in study 520. A total of 34.5% of all patients previously used one anticholinergic, 27.0% previously used two anticholinergics, 18.0% previously used three anticholinergics, 9.8% previously used four anticholinergics, 5.7% previously used five anticholinergics, and 5.1% previously used five or more anticholinergics. The mean duration of prior anticholinergic use was approximately 2.4 years (range: 0.3 weeks to 1,058.6 weeks) in study 095, and 2.1 years (range: 2 weeks to 857.3 weeks) in study 520 (Table 5).

In study 077, the majority of patients were Caucasian. The duration of OAB ranged from 0.7 to 30.2 years in the Ona A group, and from 1.5 to 47.6 years in the placebo group. The mean weekly frequency of urge-incontinence episodes at baseline ranged from 27.8 to 32.5. The mean weekly frequency of micturition episodes at baseline ranged from 73.3 to 80.3 (Table 4). In study P030438, the mean daily frequency of urge-incontinence episodes at baseline was around 5.9 (Table 4); data on duration of disease, micturition, or race were not reported in this study. Data on the previous use of anticholinergics medications were not reported for either of the phase 2 studies.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	191622-095		191622-520		191622-077		P030438	
	Ona A 100 U (N = 280)	Placebo (N = 277)	Ona A 100 U (N = 277)	Placebo (N = 271)	Ona A 100 U (N = 54)	Placebo (N = 44)	Ona A 100 U (N = 22)	Placebo (N = 29)
Age, mean (SD)	61.7 (12.7)	61.0 (13.1)	59.5 (15.5)	59.2 (14.1)	60.8 (12.1)	58.7 (12.3)	62.5 (SE 17.5)	61.7 (SE 13.9)
Age ≥ 65 years, N (%)	121 (43.2)	117 (42.2)	124 (44.8)	108 (39.8)	23 (42.6)	13 (29.5)	NR	NR
Female, N (%)	252 (90.0)	245 (88.4)	244 (88.1)	229 (84.5)	50 (92.6)	40 (90.9)	18 (81.8)	27 (93.1)
Race, n (%)								
Caucasian	230 (82.1)	241 (87.0)	270 (97.5%)	263 (97.0%)	48 (88.9)	39 (88.6)	NR	NR
Non-Caucasian	50 (17.9)	36 (13.0)	7 (2.5%)	8 (3.0%)	6 (11.1)	5 (11.4)	NR	NR
Weight, kg, mean (SD)	83.4 (18.6)	83.8 (22.1)	77.7 (17.0)	80.9 (19.7)	79.2 (20.8)	78.8 (16.9)	NR	NR
Duration of OAB								
Mean years (SD)	6.8 (7.7)	6.6 (7.4)	5.2 (6.3)	5.7 (6.7)	NR	NR	NR	NR
Range	0.5 to 64.4	0.5 to 60.2	0.5 to 50.9	0.5 to 50.4	0.7 to 30.2	1.5 to 47.6	NR	NR
Incontinence episodes/24 hours, mean (SD)	5.5 (3.6)	5.1 (3.2)	5.5 (3.8)	5.7 (3.9)	NR	NR	NR	NR
Urge-incontinence episodes/24 hours, mean (SD)	4.8 (3.2)	4.5 (3.1)	5.1 (3.7)	5.2 (3.7)	NR	NR	5.9 (SE 6.3)	5.9 (SE 4.6)
Urge-incontinence episodes/week, mean (SD)	NR	NR	NR	NR	27.8 (22.7)	32.5 (20.2)	NR	NR
Micturitions/24 hours, mean (SD)	12.0 (4.3)	11.2 (3.1)	12.0 (4.0)	11.8 (3.6)	NR	NR	NR	NR
Micturitions/week, mean (SD)	NR	NR	NR	NR	80.3 (22.6)	73.3 (23.0)	NR	NR
Urgency/24 hours, mean (SD)	8.5 (4.7)	7.9 (3.7)	9.1 (4.6)	8.8 (4.5)	NR	NR	8.7 (SE 6.1)	7.0 (SE 3.5)
Urgency/week, mean (SD)	NR	NR	NR	NR	69.9 (28.2)	62.0 (26.6)	NR	NR
Nocturia/24 hours, mean (SD)	2.2 (1.5)	2.0 (1.3)	2.2 (1.5)	2.1 (1.5)	NR	NR	NR	NR
Nocturia/week, mean (SD)	NR	NR	NR	NR	13.9 (6.9)	12.3 (8.2)	NR	NR
Volume voided/micturition, mean mL (SD)	156.4 (63.2)	161.1 (68.6)	144.2 (57.5)	152.6 (59.3)	155.3 (77.13)	156.1 (62.41)	144.6 (SE 54.5)	207.5 (SE 152.8)
PVR, mean mL (SD)	27.7 (30.0)	24.9 (26.9)	17.2 (23.1)	13.8 (20.6)	19.3 (29.31)	20.6 (26.16)	6.9 (SE 13.5)	7.3 (SE 13.1)

NR = not reported; OAB = overactive bladder; Ona A = onabotulinumtoxinA; PVR = post-void residual; SD = standard deviation; SE = standard error.
Source: Study 191622-520 Clinical Study Report,[20] study 191622-095 Clinical Study Report,[21] study 191622-077 Clinical Study Report,[22] Chapple et al.,[17] Nitti et al.,[16] Fowler et al.,[26] Denys et al.[19]

TABLE 5: PRIOR ANTICHOLINERGIC MEDICATIONS

	191622-095		191622-520		191622-077		P030438	
	Ona A 100 U (N = 280)	**Placebo (N = 277)**	**Ona A 100 U (N = 277)**	**Placebo (N = 271)**	**Ona A 100 U (N = 54)**	**Placebo (N = 44)**	**Ona A 100 U (N = 22)**	**Placebo (N = 29)**
Duration of prior anticholinergic medication use (years)								
N	274	274	276	271	NR	NR	NR	NR
Mean (SD)	2.6 (3.2)	2.3 (2.5)	2.2 (2.7)	2.1 (2.9)	NR	NR	NR	NR
Range	0.006 to 20.4	0.02 to 15.9	0.04 to 16.2	0.04 to 16.5	NR	NR	NR	NR
Number of prior anticholinergics taken								
N	276	274	276	271	NR	NR	NR	NR
Mean (SD)	2.4 (1.6)	2.5 (1.6)	2.3 (1.5)	2.5 (1.5)	NR	NR	NR	NR
Range	1 to 9	1 to 9	1 to 7	1 to 8	NR	NR	NR	NR
1	100 (36.2%)	88 (32.1%)	102 (37.0%)	88 (32.5%)	NR	NR	NR	NR
2	66 (23.9%)	72 (26.3%)	85 (30.8%)	73 (26.9%)	NR	NR	NR	NR
3	51 (18.5%)	52 (19.0%)	43 (15.6%)	52 (19.2%)	NR	NR	NR	NR
4	31 (11.2%)	27 (9.9%)	16 (5.8%)	33 (12.2%)	NR	NR	NR	NR
5	15 (5.4%)	17 (6.2%)	15 (5.4%)	15 (5.5%)	NR	NR	NR	NR
> 5	13 (4.7%)	18 (6.6%)	15 (5.4%)	10 (3.7%)	NR	NR	NR	NR

NR = not reported; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Study 191622-520 Clinical Study Report,[20] study 191622-095 Clinical Study Report.[21]

3.2.3 Interventions

According to treatment-group assignment, patients in the two phase 3 studies received vials of Ona A 100 U or placebo, while those in study 077 received vials of Ona A 50 U, 100 U, 150 U, 200 U, 300 U, or placebo. The investigational materials of Ona A or placebo were packaged and labelled in vials that appeared identical and were prepared by an independent drug reconstitutor. Under cystoscopic guidance, a total 20 injections of 0.5 mL each, approximately 1 cm apart and 2 mm deep, were injected into the detrusor, avoiding the trigone and the dome.

Patients in study P030438 received vials of Ona A 50 U, 100 U, 150 U, or placebo. Under cystoscopic guidance, a total of 15 homogeneously distributed injections were performed into the detrusor, avoiding the trigone.

For studies 095 and 520, patients were allowed to receive a second treatment if the following pre-defined re-treatment criteria were met: patients had to initiate the request for treatment 2; patient experienced two or more urge-incontinence episodes, with no more than one urge incontinence–free day, as recorded in a three-day diary in the week prior to the qualification for treatment 2 visit; a minimum of 12 weeks had elapsed since the previous treatment and a maximum of 27 weeks since randomization; and a post-void residual urine volume < 200 mL. Only one additional treatment was allowed for both studies. All patients who were eligible for the second treatment received Ona A 100 U. In the phase 2 studies 077 and P030438, patients received only one cycle of treatment upon study entry; no re-treatment was allowed throughout the study.

In studies 095, 520, and 077, anticholinergics or any other medications (including sympathomimetic medications) used for the treatment of symptoms of OAB were prohibited before study treatment was received and throughout study participation. However, in study P030438, for patients who were receiving anticholinergic therapy at the start of the study, a stable regimen was maintained during the study period.

3.2.4 Outcomes

For the phase 3 studies 095 and 520, the co-primary efficacy outcomes were the proportion of patients who had a positive treatment response on the treatment benefit scale and the change from baseline in daily average frequency of incontinence episodes at the primary end point (week 12) (frequency of incontinence episodes was measured by patients using a three-day bladder diary during the 21 days preceding randomization and during the three days preceding each scheduled clinic visit). The patient's three-day bladder diary also measured micturition episodes, urgency episodes, and nocturia episodes. There were four secondary efficacy outcomes: the change from baseline in daily average frequency of micturition episodes, the change from baseline in daily average frequency of urgency episodes, Incontinence Quality of Life Questionnaire (I-QOL) total score, and King's Health Questionnaire (KHQ) domain scores for role limitations and social limitations. Patients' quality of life was also assessed using the 12-Item Short-Form Health Survey (SF-12) and other domain scores of the KHQ. Other efficacy analyses assessed were the change from baseline in nocturia episodes, the change from baseline in urge-incontinence episodes, duration of treatment effect, and the proportion of patients achieving a 50% or greater reduction from baseline, or a 100% reduction from baseline, in incontinence episodes and in urge-incontinence episodes. Study baseline values were determined based on the three-day bladder diary completed during the 21 days preceding randomization (screening period). If re-treatment was received, patients were followed for at least 12 weeks after treatment 2, but not exceeding 39 weeks after the initial treatment.

In study 077, the primary efficacy outcome was the change from baseline in weekly frequency of urge-incontinence episodes at the primary end point (week 12) as measured by the patient bladder electronic diary (e-diary) during the seven consecutive days throughout the screening period and during the seven consecutive days preceding each scheduled visit. The e-diary also captured micturition episodes, nocturia episodes, and urgency episodes. Secondary efficacy outcomes included the change from baseline in the weekly frequency of micturition, urgency, and nocturia episodes, and proportion of patients achieving various thresholds of change from baseline in incontinence episodes. Patients' quality of life was also assessed using KHQ (symptoms component only), I-QOL, and the European Quality of Life Scale Visual Analogue Scale (EQ-VAS). Study baseline values were determined based on the diary completed by the patient for seven consecutive days prior to randomization.

In study P030438, the primary efficacy outcome was the proportion of patients achieving > 50% reduction, compared with baseline, of both urgency and urge-incontinence episodes at month three. Bladder function outcomes were captured in a micturition diary completed by patients over three days during the 15 days preceding inclusion (baseline), at day eight, and at months one, three, five, and six. Secondary outcomes included micturition episodes, urge-incontinence episodes, urgency episodes, I-QOL, and EQ-VAS.

Health-related quality of life (HRQoL) scales used in the trials are described below.

The standard version of KHQ is a 21-item disease-specific questionnaire that has been developed and validated for participants with urinary incontinence.[27] The KHQ consists of nine domains: general health perceptions, impact on life, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, and incontinence severity measures. Item scores are converted to a standardized scale. Scores for the KHQ domains range from 0 to 100, where 0 indicates the best outcome or response and 100 indicates the worst outcome or response.[27] A within-group minimal clinically important difference (MCID) of 5 points has been reported for each domain in patients with OAB.[28,29] (See APPENDIX 5: VALIDITY OF OUTCOME MEASURES for additional information regarding the description and validation of the KHQ.)

The I-QOL measure is used in patients with chronic urinary incontinence (i.e., urge, stress, and mixed) to assess the impact of incontinence on HRQoL.[30,31] The I-QOL is a 22-item scale consisting of three domains: avoidance and limiting behaviour (eight items), psychosocial impacts (nine items), and social embarrassment (five items).[31] Each item is scored according to a 5-point scale (1 = extremely and 5 = not at all).[28] Scores (range: 0 to 100) are calculated for each domain along with an overall composite score for the 22 items. The higher the I-QOL score, the higher the quality of life and the lower the impact of incontinence on HRQoL.[28,31] No MCID has been reported for non-stress incontinence, while the between-treatment MCID for the total I-QOL score in stress incontinence has been reported to be 2.5 points.[32] (See APPENDIX 5: VALIDITY OF OUTCOME MEASURES for additional information regarding the description and validation of the I-QOL.)

The SF-12 consists of 12 items from the SF-36, which are scored and weighted to obtain two summary scores: one for physical health (the physical component summary [PCS]) and one for mental health (the mental component summary [MCS]).[33,34] However, no published MCIDs could be found for the SF-12 (or 36-item health survey, the SF-36) for OAB or urinary incontinence. (See APPENDIX 5: VALIDITY OF OUTCOME MEASURES for additional information regarding the description and validation of the SF-12.)

The EQ-VAS is a 20 cm visual analog scale that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. No published MCIDs could be found for OAB or urinary incontinence for the EQ-VAS. (See APPENDIX 5: VALIDITY OF OUTCOME MEASURES for additional information regarding the description and validation of the EQ-VAS.)

For studies 095, 520, and 077, adverse events were defined as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether related to the investigational product or not. Serious adverse events were events that were fatal, life-threatening, or required hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability or a congenital anomaly or birth defect, or were an important medical event. For studies 095, 520, safety data were presented for the 12-week double-blind treatment phase only; long-term safety and tolerability data are presented from the open-label extension phase in APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY. For study P030438, safety and tolerability data were evaluated at each visit; no definition for harms outcomes was provided.

3.2.5 Statistical Analysis

Trials 095 and 520 had a power of 82% to detect a between-group difference (Ona A 100 U versus placebo) of 2.3 episodes per day in change from baseline in the number of incontinence episodes at a significance level of 0.05. In addition, the number of patients included per treatment group provided the trials with 89% power to detect a difference of 3.6 episodes in change from baseline in micturition. Trial 077 had a power of 61% to 92% to detect a between-group difference of four to six episodes in change from baseline in weekly frequency of urge-incontinence episodes at a significance level of 0.05. Study P030438 had a power of 62% to detect a reduction of greater than 50% compared with baseline of both urgency and urge-incontinence episodes at month three at a significance level of 0.05.

In studies 095 and 520, all efficacy outcomes were analyzed using an analysis of covariance (ANCOVA). The statistical model included treatment group as the main effect, with baseline value and site as covariates. The treatment effect on incontinence and urge incontinence was also analyzed as the proportion of patients with a ≥ 30%, 50%, 75%, and 100% decrease from baseline in the number of incontinence or urge-incontinence episodes per day using the Cochran–Mantel–Haenszel method. The time to request re-treatment was estimated using the Kaplan–Meier survival method, and between-group comparisons were performed using a log-rank test.

To adjust for multiple comparisons in studies 095 and 520, a hierarchical testing strategy was used that started with the primary efficacy end point followed by testing of the secondary end points, in which the test of any lower-ranked secondary end point was not considered statistically significant if the *P* value of a higher-ranked secondary end point was > 0.05. The hierarchical order of the secondary end points was frequency of incontinence episodes, treatment benefit scale, frequency of micturition episodes, I-QOL total score, KHQ domain scores, and frequency of urgency episodes.

For all other efficacy analyses, a two-sided test with *P* value ≤ 0.05, unadjusted for multiplicity, was considered by the manufacturer to be statistically significant. Missing values on the episodes of incontinence were imputed using the last observation carried forward (LOCF) approach. Missing values for I-QOL total scores were imputed if three or fewer items were missing, using the mean value of the non-missing items within the same domain. Missing items for I-QOL domain scores and multi-item domains of the KHQ were imputed if at least half of the items in the domain had non-missing responses,

by using the mean value of responses to other items within the same domain. Missing values for single-item domains of the KHQ and other efficacy outcomes were not imputed.

For study 077, all efficacy outcomes were analyzed using an ANCOVA. The statistical model included treatment group and investigator as factors, and baseline outcome value as covariates. Unlike the phase 3 studies, no adjustment for multiplicity was made in this study. Missing values for urge incontinence were imputed using the last observation adjusted by the ratio of means for the previous and current visit over all non-missing values for all patients. Missing values for health outcome data were adjusted in a manner similar to the adjustments made for health outcomes in studies 095 and 520. Missing values for other efficacy outcomes were not imputed.

Between-treatment comparisons in study P030438 were performed using the Kruskal–Wallis test (for quantitative variables) and the $\chi 2$ test (for qualitative variables). Missing values were imputed using the LOCF approach. No adjustment for multiplicity was made in this study.

The CDR protocol included a subgroup by age (< 65 years of age versus ≥ 65 years of age); however, such analysis was undertaken only in studies 095 and 520 for the co-primary end points.

a) Analysis Populations

For studies 095, 520, and 077, the primary analysis population used for efficacy and health outcomes was the intention-to-treat (ITT) analysis set. The various analyses populations are defined below.

- ITT analysis set: patients were analyzed according to the randomization assignment, regardless of actual treatment received. Missing values were imputed for the primary efficacy analyses as described previously.
- Per-protocol (PP) analysis set: PP population included all randomized patients with no major protocol violations. The PP analyses were based on observed data with no imputation for missing values. The PP population was used for confirmatory analyses of primary efficacy analyses.
- Safety analysis set: safety analyses were based on the treatment actually received by each patient and were performed using the safety population, consisting of all patients who received the study treatment at Day 0.

For study P030438, analysis populations were not defined; however, it seems that patients with a protocol violation were excluded from the analyses.

3.3 Patient Disposition

The disposition of participants in the included studies is presented in Table 6.

The proportion of patients who withdrew from studies 095 and 520 prior to week 12 was 6.1% and 4.9%, respectively. More patients were likely to withdraw due to adverse events in the Ona A group than placebo group (1.4% versus 0.7%, and 1.4% versus 0.4% in studies 095 and 520, respectively). In study 077, the proportion of patients who withdrew during the 36-week study period was 13.3%, with the most common reason for discontinuation in the Ona A group being lack of efficacy (5.6%), and "other" (9.1%) in the placebo group. The reasons for withdrawal are described in Table 6.

Patient disposition was not provided for study P030438.

TABLE 6: PATIENT DISPOSITION

	191622-095		191622-520		191622-077		P030438	
	Ona A 100 U	Placebo	Ona A 100 U	Placebo	Ona A 100 U	Placebo	Ona A 100 U	Placebo
Screened, N	NR		NR		711		131	
Randomized total N	557		548		313		107	
Randomized, N	280	277	277	271	54	44	23	31
Treated, N (%)	278	272	274	270	55	43	NR	NR
Discontinued, N (%)	13 (4.6)	21 (7.6)	11 (4.0)	16 (5.9)	6 (11.1)	7 (15.9)	NR	NR
Reasons for discontinuation								
Adverse event	4 (1.4)	2 (0.7)	4 (1.4)	1 (0.4)	0 (0.0)	1 (2.3)	NR	NR
Lack of efficacy	1 (0.4)	0	1 (0.4)	0	3 (5.6)	1 (2.3)	NR	NR
Pregnancy	1 (0.4)	0	0	0	0 (0.0)	0	NR	NR
Lost to follow-up	2 (0.7)	0	1 (0.4)	2 (0.7)	1 (1.9)	0	NR	NR
Personal reasons	3 (1.1)	11 (4.0)	3 (1.1)	7 (2.6)	1 (1.9)	1 (2.3)	NR	NR
Protocol violation	0	6 (2.2)	2 (0.7)	4 (1.5)	1 (1.9)	0	NR	NR
Other	2 (0.7)	2 (0.7)	0	2 (0.7)	0	4 (9.1)	NR	NR
ITT, N[a]	280	277	277	271	54	44	NR	NR
PP, N[b]	244	234	248	241	48	34	22	29
Safety, N[c]	278	272	274	270	55	43	22	29

ITT = intention-to-treat; Ona A = onabotulinumtoxinA; PP = per-protocol.
[a] All randomized patients.
[b] Includes all randomized patients with no major protocol deviations during the placebo-controlled phase.
[c] All patients who received at least one dose of study medication.
Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report;[21] Study 191622-077 Clinical Study Report;[22] Denys et al.[19]

3.4 Exposure to Study Treatments

Drug exposure was similar across treatment groups in studies 077 and P030438, as all patients received only a single treatment. Duration of exposure in studies 095 and 520 differed between patients and between treatment groups, as patients may have received a second treatment or exited the study; however, since only the controlled comparison is reported in this review, drug exposure was similar across treatment groups for the first 12 weeks and limited to only one treatment.

3.5 Critical Appraisal

3.5.1 Internal Validity

- Studies 095, 520, and 077 used appropriate methods to conceal allocation and randomize patients to treatment groups using an interactive voice response system. Blinding was achieved by using vials that appeared identical and were prepared by an independent drug reconstitutor. The methods reported for study P030438 for allocation concealment, randomization, and blinding were not explicitly stated.
- Patients used a bladder diary to record incontinence data (e.g., number of episodes of incontinence over a 24-hour period). Therefore, there is a degree of subjectivity in the frequency outcome reported in the trials, although it is unlikely, in the context of a double-blind trial, that there would be a systematic difference between the Ona A and placebo groups.

- Study P030438 did not report details of how urgency was defined, whereas studies 095, 520, and 077 used a standardized scale to evaluate this subjective outcome. It is therefore difficult to compare the urgency episode results across studies.
- For studies 095 and 520, the primary efficacy analysis of the included trials was based on an ITT population with missing values on incontinence episodes imputed using a LOCF approach. For example, at week six, the missing values on the frequency of incontinence episodes were imputed using the available data at week two; likewise, the missing values at week 12 on frequency of incontinence episodes were imputed using the available observations at week six. However, imputing a frequency of incontinence with values observed at least four or six weeks apart may not be appropriate given that the patient's incontinence status could be highly varied between the two time points. But when sensitivity analysis using "observed data" without imputing for missing values was performed, there was no change in the direction of results. Similarly, in studies 077 and P030438, missing values for primary outcomes were imputed, but when sensitivity analysis using "observed data" without imputing for missing values was performed, no change in the direction of results was found.
- By study design, the comparative efficacy and safety analysis for studies 095 and 520 is restricted to 12 weeks following a single treatment. After week 12, patients in the Ona A group could receive a second treatment, and patients in the placebo group could be treated with Ona A. This strategy is reflective of "real-world" practices in which patients may receive re-treatment in case of inadequate response or waning of effect following the initial treatment, and is also ethically valid as it allowed placebo-treated patients to receive active therapy. However, such a design makes it difficult to assess the safety, efficacy, and duration of treatment effect after week 12 due to the lack of a true placebo control group.
- In studies 095 and 520, a hierarchical analysis strategy for four ranked secondary outcomes was used to control the type 1 error rate for multiple secondary end points, in which the test of any lower-ranked secondary end point was not considered statistically significant if the *P* value of a higher-ranked secondary end point was not ≤ 0.05. The problem with this approach is that only certain outcomes were selected; hence, the hierarchical approach did not take into consideration all outcomes measured, including domain scores for I-QOL, some domain scores for the KHQ, and the SF-12. As a consequence, the interpretations of the findings on quality of life were compromised. From a health technology assessment perspective, any improvements on these quality of life outcomes are important considerations with regard to the beneficial effects of the drug in the treatment of refractory OAB symptoms. In addition, no rationales were provided on how the hierarchical testing outcomes were ranked. No adjustment for multiplicity was made in this study for studies 077 and P030438.
- In study P030438, anticholinergic use was permitted in the included trials for patients who used these drugs prior to the study. However, compliance data were not provided. It is possible that compliance with these drugs was lower in the Ona A group compared with placebo due to the higher efficacy of Ona A. Lower compliance with anticholinergics could result in a degree of underestimation of the benefit of Ona A on urge incontinence and urgency frequency compared with placebo. Underestimation of the incidence of adverse effects in the Ona A group is also possible.

3.5.2 External Validity

- Patient populations in the phase 3 studies had a daily frequency of incontinence episodes ranging from 5.1 to 5.7 at baseline in studies 095 and 520. According to the clinical expert consulted for this review, the patients enrolled in both trials had more severe symptoms than those in usual clinical practice, as they have had a higher incontinence frequency than would be typically encountered in

the target population in clinical practice. Thus, the results of these two trials are most directly generalizable to a relatively severely affected patient population.

- Ona A is indicated for the treatment of OAB with symptoms of incontinence, urgency, and frequency in adults who have inadequate response to or are intolerant of anticholinergic therapies. In the phase 3 studies and study 077, patients' inadequate response to one or more anticholinergic treatments was based on the judgment of the investigators, with no specific response criterion or threshold identified. On the one hand, the lack of a definition of inadequate response is generalizable, since there was considerable heterogeneity in the definition of treatment response.[35,36] However, this aspect of the studies is also likely to introduce a degree of variability in the population enrolled, as well as an element of uncertainty as to which patients should receive Ona A in clinical practice.
- Approximately 90% of the patient populations included in the trials were women, which might not reflect what is seen in clinical practice.
- The 12-week trials were considered to be of sufficient duration to observe a treatment effect, but are insufficient for consideration of long-term efficacy and safety.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in this section (see Section 2.2, Table 2). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

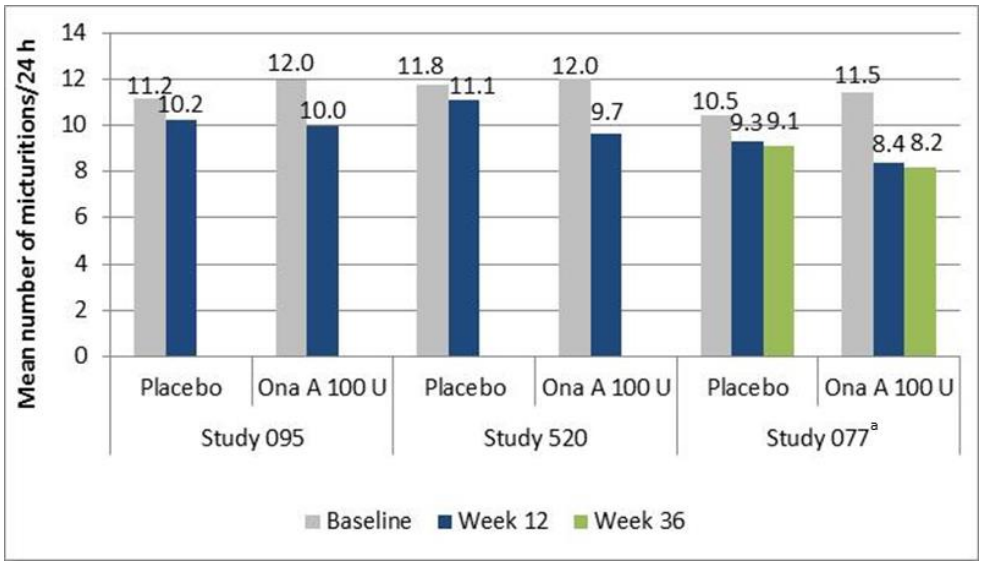
3.6.1 Micturition Episodes

At baseline, the mean number of micturitions per 24 hours in studies 095 and 520 ranged from 11.2 to 12.0 and was similar within and between studies (Figure 2 and Appendix 4, Table 8). All treatment groups reported a reduction in the mean daily frequency of micturition episodes at week 12 (placebo 0.63 to 0.98; Ona A 2.01 to 2.35). Compared with placebo, patients treated with Ona A had a statistically significantly greater reduction from baseline in daily frequency of micturition episodes at week 12, with a mean difference of –1.04 (95% confidence interval [CI], –1.48 to –0.59) in study 095, and –1.72 (95% CI, –2.19 to –1.26) in study 520. *P* values for between-group differences at week 12 were < 0.001 in both studies (Appendix 4, Table 8).

At baseline, the mean weekly frequency of micturition episodes in study 077 was 73.3 for placebo and 80.3 for Ona A (Figure 2 and Appendix 4, Table 8). Both treatment groups reported a reduction in the mean weekly frequency of micturition episodes at week 12 (8.3 for placebo versus 21.7 for Ona A) and week 36 (9.3 for placebo versus 22.9 for Ona A). Mean changes from baseline were not statistically significantly different between Ona A and placebo at week 12 ($P = 0.053$), but were statistically significantly different at week 36 ($P = 0.05$).

Frequency of micturition episodes was not reported for study P030438 at baseline or at 90- or 180-day end points. However, the *P* value for the between-group difference indicated that, compared with placebo, patients treated with Ona A had a statistically significantly greater reduction from baseline in number of micturitions per 24 hours after 90 days of receiving the treatment ($P < 0.001$) but not at 180 days.

FIGURE 2: MICTURITION FREQUENCY



Ona A = onabotulinumtoxinA.
[a] Daily frequency of micturition episodes for study 077 were calculated by CADTH from the reported mean weekly frequency of the micturition episodes.

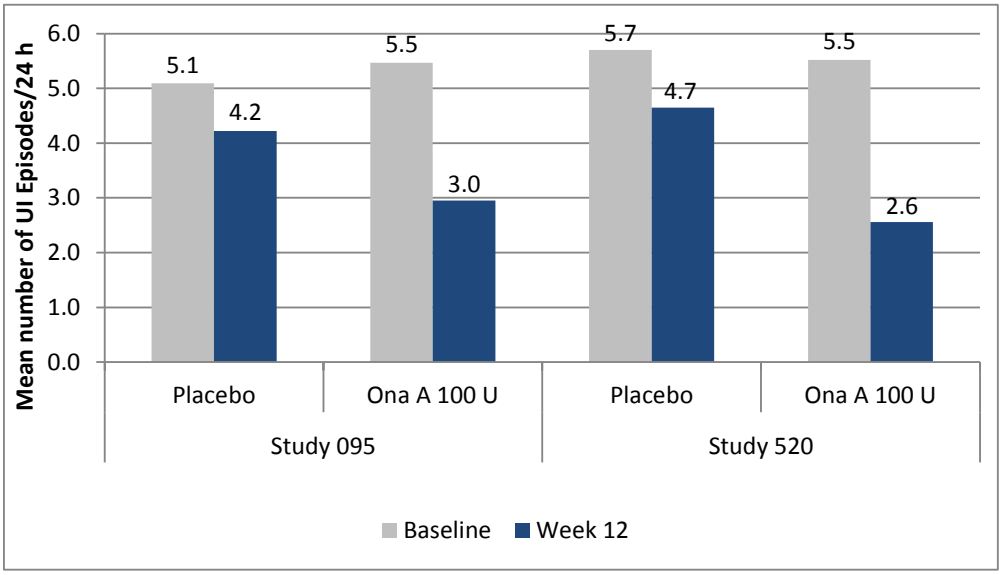
3.6.2 Incontinence Episodes

At baseline, the mean number of daily incontinence episodes in studies 095 and 520 ranged from 5.1 to 5.7 and was similar within and between studies (Figure 3 and Appendix 4, Table 9). All treatment groups reported a reduction in the mean daily frequency of incontinence episodes at week 12 (placebo 0.87 to 1.05; Ona A 2.52 to 2.96). Patients treated with Ona A had a statistically significantly greater reduction from baseline in daily frequency of incontinence episodes at week 12, with a mean difference of −1.65 (95% CI, −2.13 to −1.17) in study 095, and −1.91 (95% CI, −2.43 to −1.39) in study 520. *P* values for between-group differences were < 0.001 in both studies (Appendix 4, Table 9).

Subgroup data by age (< 65 versus ≥ 65) were available for studies 095 and 520 (Appendix 4, Table 10). The difference between Ona A and placebo was statistically significantly different for both subgroups, and results were generally consistent with the results for the entire population.

No results for incontinence episodes were reported for studies 077 and P030438.

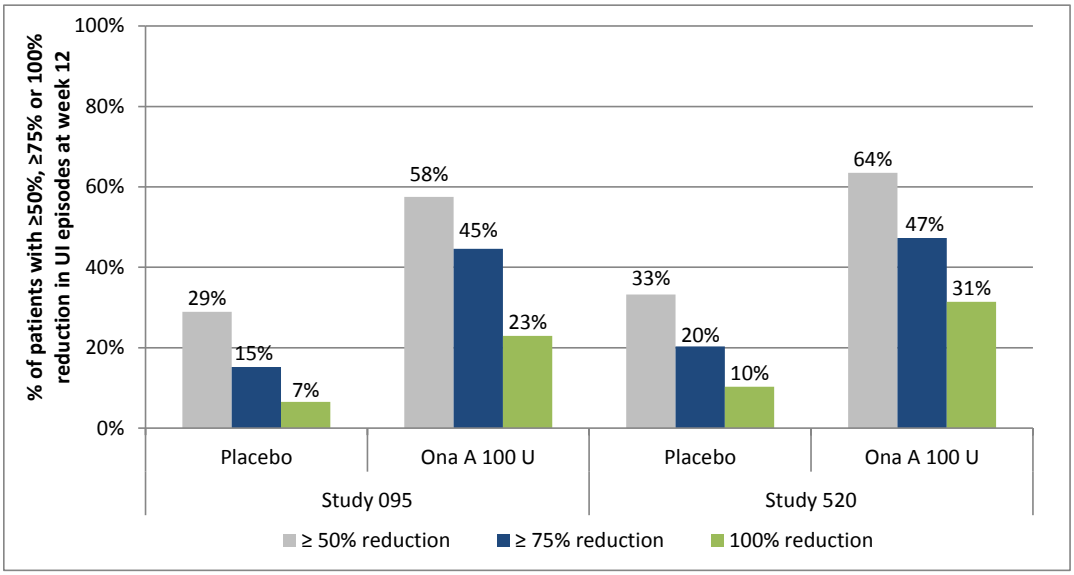
FIGURE 3: INCONTINENCE EPISODES



UI = urinary incontinence.

The percentage of patients with ≥ 50%, ≥ 75%, or a 100% reduction from baseline in daily incontinence episodes at week 12 was also reported for studies 095 and 520. In both studies, compared with the placebo group, there was a significantly higher percentage of patients in the Ona A group who achieved a reduction of ≥ 50%, ≥ 75%, or 100% from baseline in incontinence episodes (Figure 4 and Appendix 4, Table 9).

FIGURE 4: PERCENTAGE OF PATIENTS WITH A ≥ 50%, ≥ 75%, OR 100% REDUCTION IN INCONTINENCE EPISODES AT WEEK 12



UI = urinary incontinence.

3.6.3 Urge-Incontinence Episodes

The results for urge incontinence in studies 095 and 520 were similar to those for incontinence episodes, showing statistically significant between-treatment differences favouring Ona A over placebo (Appendix 4, Table 11).

At baseline, the mean weekly frequency of urge-incontinence episodes in study 077 was 27.8 for placebo and 32.5 for Ona A (Appendix 4, Table 11). Mean changes from baseline were not statistically significantly different between Ona A and placebo at week 12 nor at week 36. The percentage of patients with ≥ 50%, ≥ 75%, or a 100% reduction from baseline in weekly urge-incontinence episodes at week 12 were also reported for study 077. A statistically significantly higher percentage of patients achieved a reduction of ≥ 50% and ≥ 75% from baseline in urge-incontinence episodes in the Ona A group compared with the placebo group at week 36, but not at week 12. Compared with placebo, a statistically significantly higher percentage of patients achieved a 100% reduction in urge incontinence in the Ona A group at week 12 and week 36 (Appendix 4, Table 11).

At baseline, the mean daily frequency of urge-incontinence episodes in study P030438 was 5.9 for both the placebo and Ona A groups. The percentage of patients with ≥ 50% (primary end point) and ≥ 75% improvement from baseline of both urgency and urge-incontinence episodes at month three were reported. No statistically significant difference was found between Ona A 100 U and placebo for either ≥ 50% or ≥ 75% improvement of urgency and urge-incontinence episodes at month three.

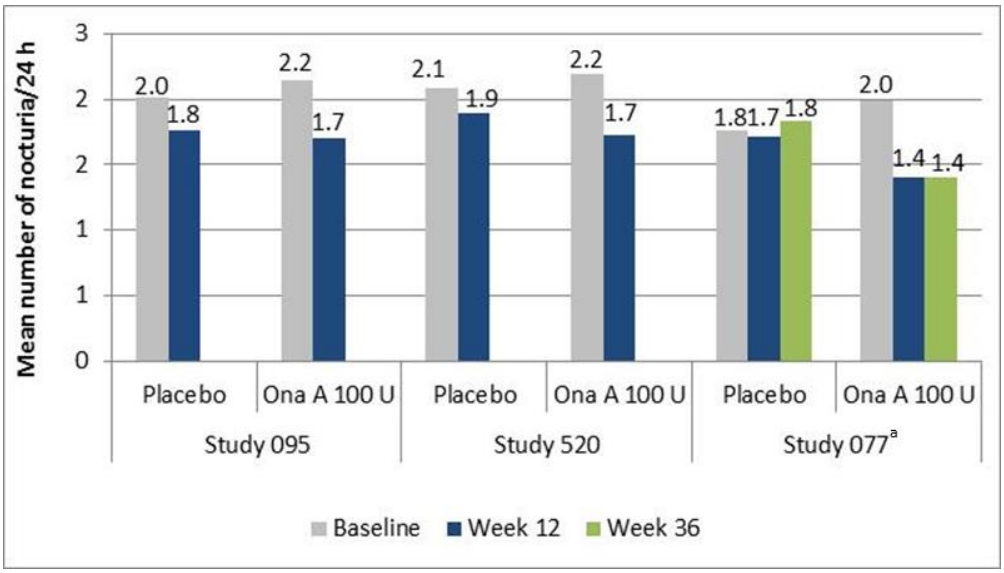
3.6.4 Nocturia Episodes

At baseline, the mean number of nocturia episodes per 24 hours in studies 095 and 520 ranged from 2 to 2.2 and was similar within and between studies (Figure 5 and Appendix 4, Table 12). All treatment groups reported a reduction in the mean daily frequency of nocturia episodes at week 12 (placebo 0.18 to 0.25; Ona A 0.45 to 0.46). Patients treated with Ona A had a statistically significantly greater reduction from baseline in daily frequency of nocturia episodes at week 12, with a mean difference of −0.20 (95% CI, −0.38 to −0.02) in study 095, and −0.27 (95% CI, −0.47 to −0.08) in study 520. *P* values for between-group differences at week 12 were 0.029 and 0.007 for studies 095 and 520, respectively (Appendix 4, Table 12).

At baseline, the mean weekly frequency of nocturia episodes in study 077 was 12.3 for placebo and 13.9 for Ona A (Figure 5 and Appendix 4, Table 12). Both treatment groups reported a reduction in the mean weekly frequency of nocturia episodes at week 12 (0.3 for placebo versus 4.1 for Ona A), but only Ona A group reported reduction in weekly frequency of nocturia episodes at week 36. Mean changes from baseline were not statistically significantly different between Ona A and placebo at week 12 or week 36.

No results for nocturia episodes were reported for study P030438.

FIGURE 5: NOCTURIA EPISODES



Ona A = onabotulinumtoxinA.
[a] Daily frequency of nocturia episodes for study 077 were calculated by CADTH from the reported mean weekly frequency of the nocturia episodes.

3.6.5 Urgency Episodes

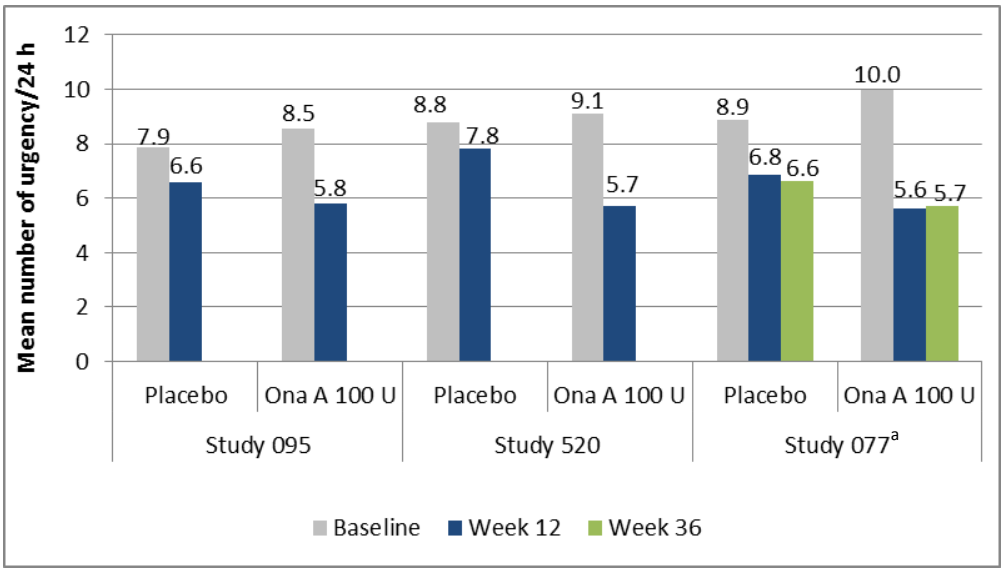
In studies 095 and 520, the number of urgency episodes was based on a "yes" response to the diary question, "Was this episode associated with a sudden and urgent need to urinate?", while in study 077 it was based on a "yes" response to a question asking if urgency was associated with micturition or nocturia episodes. In study P030438, it was unclear how urgency, a subjective outcome, was defined and measured.

At baseline, the mean number of urgency episodes per 24 hours in studies 095 and 520 ranged from 7.9 to 9.1 (Figure 6 and Appendix 4, Table 13). All treatment groups reported a reduction in the mean daily frequency of urgency episodes at week 12 (placebo 0.95 to 1.26; Ona A 2.76 to 3.39). Patients treated with Ona A had a statistically significantly greater reduction from baseline in daily frequency of urgency episodes at week 12, with a mean difference of −1.51 (95% CI, −2.14 to −0.87) in study 095, and −2.44 (95% CI, −3.09 to −1.79) in study 520. *P* values for between-group differences were < 0.001 in both studies (Appendix 4, Table 13).

At baseline, the mean weekly frequency of urgency episodes in study 077 was 62.0 for placebo and 69.9 for Ona A 100 U (Figure 6 and Appendix 4, Table 13). Both treatment groups reported a reduction in the mean weekly frequency of urgency episodes at week 12 (14.1 for placebo versus 30.9 for Ona A 100 U), and week 36 (15.1 for placebo versus 30.1 for Ona A 100 U). Mean changes from baseline were statistically significantly different between Ona A 100 U and placebo at week 12 (*P* = 0.043), but not statistically significantly different at week 36 (*P* = 0.109).

At baseline, the mean number of urgency episodes per 24 hours in study P030438 was 7.0 for placebo and 8.7 for Ona A 100 U. Data findings and specific *P* values for between-treatment testing at 90 and 180 days were not reported. However, it was reported that there were no statistically significant between-treatment differences in urgency frequency at either time points (90 or 180 days) (Appendix 4, Table 13).

FIGURE 6: URGENCY EPISODES



Ona A = onabotulinumtoxinA.
[a] Daily frequency of urgency episodes for study 077 were calculated by CADTH from the reported mean weekly frequency of the urgency episodes.

3.6.6 Time to Request Re-treatment and Proportion of Patients who Requested Re-treatment

In study 095, 81% of patients in the placebo group versus 62% of patients in the Ona A group requested re-treatment (Appendix 4, Table 14). The median time to patient request for re-treatment was statistically significantly longer in the Ona A group (21.1 weeks) compared with the placebo group (12.4 weeks; $P < 0.001$). In study 520, 85% of patients in the placebo group versus 63% of patients in the Ona A group requested re-treatment (Appendix 4, Table 14). The median time to patient request for re-treatment was statistically significantly longer in the Ona A group (19.1 weeks) compared with the placebo group (13.1 weeks; $P < 0.001$).

As per the protocol of studies 095 and 520, patients qualified for re-treatment if they met specific criteria (See Section 1.1.1). The number of patients who received re-treatment was 150 (53.6%) versus 222 (80.1%) for Ona A versus placebo in study 095, and 170 (61.4%) versus 227 (83.8%) for Ona A versus placebo in study 520. The median time to re-treatment was 24 weeks (range: 20.4 to 25.1) versus 12.6 (range: 12.3 to 13.1) for Ona A versus placebo in study 095, and 19.1 weeks (range: 18.1 to 24) versus 13.1 (range: 12.6 to 13.3) for Ona A versus placebo in study 520 (Appendix 4, Table 14).

3.6.7 Health-Related Quality of Life

a) King's Health Questionnaire

The KHQ, a validated OAB-specific HRQoL instrument, was used in studies 095, 520, and 077 (symptoms component only). Each domain on the KHQ is scored from 0 to 100 (worst). An MCID of 5 points has been identified for each domain in patients with OAB.[28,29] Data for all the domains were abstracted from the trials for studies 095 and 520 and from the symptoms component for study 077 (Appendix 4, Table 15).

In study 095, all domains except the general health perception domain showed a statistically significant between-treatment difference favouring Ona A over placebo. Patients who received Ona A treatment had a mean change from baseline scores that exceeded the established MCID of 5 points for all domains

except for general health perception, while patients receiving placebo did exceed the above-mentioned MCID for the physical limitations domain only.

In study 520, all domains showed a statistically significant between-treatment difference favouring Ona A over placebo. Patients who received Ona A treatment had a mean change from baseline scores that exceeded the established MCID of 5 points for all nine domains, while patients receiving placebo did exceed the above-mentioned MCID for the incontinence impact, role limitations, physical limitations, and sleep and energy domains only.

Utility scores were derived from the KHQ in studies 095 and 520. Improvements in utility scores were statistically significantly greater for Ona A compared with placebo; however, between-treatment differences appear minimal: 0.0 (95% CI, 0.0 to 0.0) and 0.01 (95% CI, 0.01 to 0.02) in studies 095 and 520, respectively.

In study 077, the symptoms component domain showed a statistically significant between-treatment difference favouring Ona A over placebo at week 12, but not at week 36. The observed differences from baseline met or exceeded the reported MCID for both treatment groups at weeks 12 and 36 (Appendix 4, Table 15).

b) Incontinence Quality of Life Questionnaire

I-QOL is a disease-specific, quality of life questionnaire designed to measure the impacts of incontinence. I-QOL is scored as four variables: total I-QOL summary score and its three domains (avoidance and limiting behaviour, psychosocial impacts, and social embarrassment). I-QOL was used in studies 095, 520, 077, and P030438.

Compared with placebo, Ona A significantly increased (improved) I-QOL total scores from baseline at week 12 by 14.9 (95% CI, 11.1 to 18.7) in study 095, and by 16.9 (95% CI, 13.2 to 20.6) in study 520 (Appendix 4, Table 16). These improvements exceeded the reported MCID of 2.5 points. Statistically significant increases from baseline in total I-QOL were observed in study 077 at week 12 and week 36, and in study P030438 at 90 days and 180 days.

Statistically significant increases from baseline in I-QOL individual domain scores (avoidance and limiting behaviour, psychosocial impact, and social embarrassment) were observed at week 12 in studies 095 and 520 with improvements being statistically significantly higher for Ona A treatment groups compared with the placebo groups. Similarly statistically significantly higher scores in all I-QOL individual domain scores for Ona A treatment groups compared with the placebo groups were observed in study 077 at weeks 12 and 36, and in study P030438 at 90 days and 180 days, except for the social embarrassment domain in study P030438 at 90 days.

c) Twelve-Item Short-Form Health Survey

The SF-12 summary scores (PCS, MCS) and utility scores were reported for studies 095 and 520; however, no published MCIDs could be found for the SF-12 (or SF-36) in OAB or urinary incontinence.

No statistically significant difference between Ona A and placebo was found for the change from baseline at week 12 in PCS scores for both studies. Compared with placebo, Ona A produced statistically significantly increased MCS scores from baseline at week 12: 2.6 (95% CI, 0.9 to 4.3) in study 095, and 3.6 (95% CI, 2.0, 5.1) in study 520. Similarly, compared with placebo, Ona A statistically significantly increased utility scores from baseline at week 12; however, the between-treatment difference was

minimal: 0.0 (95% CI, 0.0 to 0.0) in study 095, and 0.04 (95% CI, 0.02 to 0.05) in study 520 (Appendix 4, Table 17).

d) EQ-VAS

EQ-VAS was used in studies 077 and P030438. The EQ-VAS is a 20 cm visual analog scale that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." No published MCIDs could be found for OAB or urinary incontinence for the EQ-VAS.

In study 077, the mean changes from baseline in EQ-VAS scores were not statistically significantly different in patients treated with Ona A 100 U compared with placebo. In study P030438, the mean change from baseline in the EQ-VAS score was statistically significantly higher in Ona A 100 U compared with placebo at 90 days, but not at 180 days post-treatment (Appendix 4, Table 18).

3.7 Harms

3.7.1 Adverse Events

The proportion of patients who experienced at least one adverse event was higher in the Ona A group (61.5% in study 095, 51.8% in study 520, and 80% in study 077) than in the placebo group (52.9% in study 095, 34.1% in study 520, and 76.7% in study 077) (Table 7). Study P030438 did not report the incidence of adverse events.

The most frequent adverse events after initial treatment reported in all the included studies were UTI, urinary retention, and dysuria. In studies 095 and 520, UTI, urinary retention, and dysuria occurred more frequently in the Ona A 100 U group than in the placebo group. The percentage of patients who experienced UTI was 15.5% and 20% in the Ona A groups compared with 5.9% and 5.2% in the placebo groups in studies 095 and 520, respectively. The proportion of patients who experienced urinary retention was 5.4% and 5.8% in the Ona A groups compared with 0.4% in both placebo groups. The proportions of patients who experienced dysuria were 12.2% and 5.8% in the Ona A groups, compared with 9.6% and 3.7% in the placebo groups. Similarly, in study 077, UTI and urinary retention were reported by 36.4% and 18.2% of patients in the Ona A 100 U groups, respectively, compared with 16.3% and 2.3% of patients in the placebo groups, whereas dysuria occurred in 11.6 % of patients in the placebo group compared with 1.8% in the Ona A group.

Other adverse events that occurred in studies 095 and 520 at a higher frequency in the Ona A–treated patients when compared with placebo were bacteriuria, residual urine volume (based on the investigator's opinion and defined as the raised PVR being clinically significant but not fulfilling the definition for urinary retention), leukocyturia, sinusitis, and pollakiuria.

The incidences of anticholinergic adverse events other than urinary retention were either lower than 1% or never experienced by the patients included in the trials.

3.7.2 Serious Adverse Events

In studies 095 and 520, the proportion of patients receiving Ona A 100 U who reported at least one serious adverse event was 3.2% and 4.7% compared with 2.9% and 3.7% of patients receiving placebo (Table 7). Study 077 reported serious adverse events in 9.1% and 11.6% of patients in the Ona A 100 U and placebo groups, respectively. Study P030438 did not report serious adverse events, but they reported that 9.1% of patients in the Ona A 100 U group and 0% in the placebo group experienced at least one severe adverse event.

3.7.3 Withdrawals Due to Adverse Events

Withdrawals due to adverse events in studies 095, 520 and 077 were 1.4%, 0.7%, and 0% in Ona A–treated patients compared with 0.7%, 0.4%, and 2.3% of placebo-treated patients, respectively (Table 7). Study P030438 did not report the incidence of withdrawal due to adverse events.

3.7.4 Mortality

In studies 095 and 520, no deaths were reported during the first 12 weeks. However, in study 095, two deaths occurred after week 12 (one in the placebo group during treatment cycle 1 due to due to diverticulitis and pneumothorax, and another death in the placebo/Ona A 100 U group during treatment cycle 2 due to myocardial infarction, ventricular fibrillation, and pulmonary embolism). None of these serious adverse events were considered to be related to study treatment. In study 520, one death in the Ona A group occurred during treatment cycle 1 due to acute myocardial infarction, which was not considered to be related to study treatment. There were no deaths reported in trial 077.

3.7.5 Notable Harms

As outlined in the protocol, anaphylaxis or hypersensitivity reactions, use of CIC for urinary retention, UTI, and cardiac events were of interest for this review. Anaphylaxis or hypersensitivity reactions occurred in one patient in study 095 and one patient in study 520; both patients were in the placebo group. In studies 095, 520, 077, and P030438, the proportion of patients receiving Ona A 100 U who reported the use of CIC for urinary retention was 6.1%, 6.9%, 10.9%, and 4.5%, compared with 0%, 0.7%, 2.3% and 3.4% of patients receiving placebo.

In studies 095, 520, and 077, the proportion of patients receiving Ona A 100 U who experienced cardiac events was 0.4%, 1.1%, and 5.5%, compared with 0.7%, 0.4%, and 2.3% of patients receiving placebo. UTI events are summarized in Section 3.7.1.

TABLE 7: HARMS

	191622-095[a]		191622-520[a]		191622-077[b]		P030438	
AEs	**Ona A 100 U**	**Placebo**	**Ona A 100 U**	**Placebo**	**Ona A 100 U**	**Placebo**	**Ona A 100 U**	**Placebo**
N	278	272	274	270	55	43	22	29
Patients with > 0 AEs, N (%)	171 (61.5)	144 (52.9)	142 (51.8)	92 (34.1)	44 (80.0)	33 (76.7)		
Most common AEs[c], n (%)								
UTI	43 (15.5)	16 (5.9)	56 (20.4)	14 (5.2)	20 (36.4)	7 (16.3)	0[d]	2 (8.7)
Dysuria	34 (12.2)	26 (9.6)	16 (5.8)	10 (3.7)	1 (1.8)	5 (11.6)		
Urinary retention	15 (5.4)	1 (0.4)	16 (5.8)	1 (0.4)	10 (18.2)	1 (2.3)		
Bacteriuria	14 (5.0)	5 (1.8)	10 (3.6)	6 (2.2)	1 (1.8)	0		
Hematuria	7 (2.5)	15 (5.5)	10 (3.6)	1 (0.4)	0	6 (14.0)		
Residual urine volume	9 (3.2)	0	8 (2.9)	1 (0.4)	1 (1.8)	0		
Leukocyturia	4 (1.4)	0	7 (2.6)	2 (0.7)	NR	NR		
Sinusitis	8 (2.9)	2 (0.7)	4 (1.5)	0	2 (3.6)	2 (4.7)		
Diarrhea	7 (2.5)	5 (1.8)	3 (1.1)	4 (1.5)	2 (3.6)	1 (2.3)		
Nasopharyngitis	6 (2.2)	7 (2.6)	2 (0.7)	2 (0.7)	6 (10.9)	1 (2.3)		
Pollakiuria	6 (2.2)	3 (1.1)	3 (1.1)	1 (0.4)	1 (1.8)	0		
SAEs								
Patients with > 0 SAEs, N (%)	9 (3.2)	8 (2.9)	13 (4.7)	10 (3.7)	5 (9.1)	5 (11.6)	NR	NR
WDAEs								
WDAEs, N (%)	4 (1.4)	2 (0.7)	2 (0.7)	1 (0.4)	0 (0.0)	1 (2.3)	NR	NR
Deaths								
Number of deaths, N (%)	0	0	0	0	0	0		
AEs of special interest								
Anaphylaxis or hypersensitivity reactions	0 (0.0)	1 (0.4)	0	1 (0.4)	0	0		
Use of CIC for urinary retention	17 (6.1)[e]	0[e]	19 (6.9)[e]	2 (0.7)[e]	6 (10.9)	1 (2.3)	1 (4.5)	1 (3.4)
Cardiac events	1 (0.4)	2 (0.7)	3 (1.1)	1 (0.4)	3 (5.5)	1 (2.3)		

AE = adverse event; CIC = clean intermittent catheterization; NR = not reported; Ona A = onabotulinumtoxinA; SAE = serious adverse event; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] First 12 weeks of treatment.

[b] Adverse events that occurred in more than 1% in study 191622-095 or study 191622-520 were reported for study 191622-077.

[c] Frequency > 1% in studies 095 and 520.

[d] At month six.

[e] During treatment cycle 1 (cycle 1 defined as the period between the receipt of first treatment and second treatment, or study exit when there was no re-treatment).

Source: Study 191622-520 Clinical Study Report;[20] study 191622-095 Clinical Study Report;[21] study 191622-077 Clinical Study Report;[22] Chapple et al.;[17] Nitti et al.;[16] Dmochowski et al.;[18] Denys et al.[19]

4. DISCUSSION

4.1 Summary of Available Evidence

Three manufacturer-sponsored studies and one study sponsored by the Assistance publique – Hôpitaux de Paris were included in this review. All studies were randomized, multi-centre, double-blind, placebo-controlled trials comparing Ona A with placebo. The two phase 3 pivotal trials (study 095: n = 557; study 520: n = 548) were of up to 39 weeks' duration but the placebo-controlled comparison was limited to 12 weeks, after which all patients could receive treatment with Ona A.[16,17,20,21] The two phase 2 trials (study 077: n = 313; study P030438: n = 99) were of 36 weeks' and six months' duration, respectively.[18,19,22] Studies 095, 520, and 077 enrolled patients aged 18 years or older with symptoms of iOAB with urge incontinence and who were not adequately managed with anticholinergic therapy. The co-primary efficacy outcome in studies 095 and 520 were mean change from baseline in the number of daily incontinence episodes and the proportion of patients with a positive treatment response at week 12. The primary efficacy outcome for study 077 was mean change from baseline in the number of episodes of weekly urge incontinence. Study P030438 enrolled patients aged 18 years or older with symptoms of iOAB with three or more episodes of urgency with or without urge incontinence in a three-day period and who were refractory or had contraindications to anticholinergics, or who discontinued anticholinergics because of adverse events. The primary efficacy outcome was the proportion of patients with a > 50% reduction from baseline in both urge-incontinence and urgency episodes at three months.

Key limitations of the available evidence included the lack of trials to assess the comparative efficacy and safety of Ona A with active treatments. In addition, there was no clear definition of inadequate response to anticholinergics therapy in the trials; rather, it was based on the judgment of the investigators. Adjustments for Type I error were done for some, but not all, efficacy outcomes in studies 095 and 520, and no adjustment was done in the study to account for multiplicity in testing for studies 077 and P030438. By design, the efficacy analysis in the two phase 3 studies was restricted to the first 12 weeks; after week 12, patients in the Ona A and placebo groups could receive re-treatment if there was a loss of response but, for all patients, the treatment provided was active Ona A. Hence, there are no valid placebo-controlled data beyond 12 weeks from these trials. In addition, the phase 2 trials were dose-finding studies that included many treatment groups with non–Health Canada doses of Ona A. The number of patients treated with the Health Canada–approved dose was relatively small, and thus these studies are likely underpowered to identify important between-treatment differences for many outcomes of interest. Thus, the following discussion focuses on the results from the two phase 3 trials.

4.2 Interpretation of Results

4.2.1 Efficacy

The inclusion criteria for all four trials were consistent with the relevant Health Canada–approved indication for Ona A: adult patients with OAB with symptoms of urinary incontinence, urgency, and frequency with an inadequate response to or intolerance of anticholinergic medication. It should be noted that not all patients with OAB will suffer from urinary incontinence, but the manufacturer is specifically requesting a listing criterion for treatment of urinary incontinence. Excepting study P030438, all studies specifically enrolled patients with urinary incontinence.

The two phase 3 pivotal trials documented similar results in terms of incontinence and urge incontinence after 12 weeks; compared with placebo, Ona A reduced daily incontinence and urge-incontinence episodes by −1.7 to −1.9 and −1.7 to −2.0, respectively. In addition, a large proportion of

patients (58% to 64%) in the Ona A group achieved a ≥ 50% reduction in daily frequency of incontinence episodes by week 12 after initial treatment, compared with 29% to 33% of patients in the placebo group *(P* < 0.001). Further, 23% to 31% of patients achieved 100% continence at week 12 after Ona A treatment compared with 7% to 10% in the placebo group. While there is no known value for the change or the difference in change of incontinence or urge incontinence to be judged clinically significant, the clinical expert consulted for this review considered the observed differences between Ona A and placebo in incontinence and urge incontinence to be clinically meaningful.

In addition to the beneficial effects of Ona A in reducing the frequency of urinary incontinence (for which the manufacturer is specifically requesting reimbursement), Ona A was observed to provide reductions in other common symptoms associated with OAB. Reductions in daily micturition and urgency episodes at 12 weeks were statistically significantly greater for Ona A compared with placebo in studies 095 and 520, ranging from 1.0 to 1.7 fewer micturitions and 1.5 to 2.4 fewer urgency episodes per day. The clinical expert consulted for this review considered the reduction in urgency episodes to be a large improvement and clinically meaningful; the clinical expert also considered the reduction in micturitions to be a notable improvement but not a large treatment effect. The change from baseline at week 12 between Ona A and placebo in daily nocturia episodes in studies 095 and 520 was ≤ 0.3 episodes per day in favour of Ona A; the clinical interpretation of fractional benefits is not clear. In addition, the clinical expert indicated that this difference is not impressive on the whole. In addition to the improvements in individual OAB symptoms, studies 095 and 520 reported statistically significant and clinically important improvements in disease-specific HRQoL measures (KHQ and I-QOL) for patients treated with Ona A versus placebo. Between-treatment differences in the SF-12, while statistically significant for the MCS and utility scores, were of uncertain clinical significance.

The aforementioned study results should be interpreted in the context of the patient populations enrolled in the trials. Specifically, patients had an average frequency of approximately 5.1 to 5.7 incontinence episodes per day (36 to 40 per week), and an average frequency of urge incontinence of approximately 4.5 to 5.2 episodes per day (32 to 36 per week), which may be higher than the general OAB population with incontinence. The clinical expert consulted for this review indicated that patients with a high frequency of incontinence are the best candidates for Ona A, and that these patients represent some of the hardest patients to treat. The clinical expert also noted there is no minimum number of incontinence episodes to qualify for Ona A; rather, eligibility should relate more to refractoriness to anticholinergic drugs. However, the CDR reviewer noted that the results of the included studies may not be generalizable to a patient population with less frequent OAB symptoms.

Studies 095 and 520 are limited by the short duration (12 weeks) over which comparative efficacy can be determined. Studies 077 and P030438 provide longer-term comparative data (36 weeks and six months, respectively); however, Ona A did not demonstrate statistically significant improvements compared with placebo for many OAB symptoms at these time points. All four of the reviewed studies are limited to comparative efficacy (versus placebo) for a single treatment. However, the Health Canada–approved monograph notes that OAB patients should be considered for reinjection when the clinical effect of the previous injection has diminished, but not sooner than three months after the prior injection. Among patients randomized to Ona A in studies 095 and 520, approximately 62% requested re-treatment between weeks 12 and 24 after initial treatment, and the median time to request re-treatment was 21.1 and 18.1 weeks, respectively. However, given the design of studies 095 and 520, the randomized controlled comparison of Ona A with placebo is restricted to the effect of a single treatment over 12 weeks. Patients completing either of the phase 3 pivotal trials (study 095 or study 520) were eligible to be enrolled in an open-label extension study. Results from the long-term

extension appear to show consistent improvement from baseline in urinary incontinence, in addition to reduction in micturition, nocturia, and urgency episodes over the subsequent treatment cycles for which data are available. However, the validity of these findings is limited by the open-label non-comparative design of the extension trial.

Finally, no trials were identified that compared Ona A with other active treatments for OAB. Placebo may not be the appropriate comparator for patients with an inadequate response to anticholinergic medication, given that treatment with anticholinergic medications, while perhaps not providing sufficient or adequate response, may still provide more efficacy than placebo. In addition, for patients with an intolerance to anticholinergic medications, the recent introduction of mirabegron may provide an alternative.

4.2.2 Harms

There were no deaths during the double-blind phase in studies 095 and 520, but three deaths (two in the placebo group and one in the Ona A group) were reported in the open-label treatment phase of the included trials; however, none of these deaths were considered to be related to study treatment.

The proportion of patients who experienced adverse events, serious adverse events, and withdrawals due to adverse events was higher in the Ona A groups. Overall, the most frequent adverse events associated with Ona A were UTI, dysuria, urinary retention, bacteriuria, and increased residual urine volume. The clinical expert consulted for this review indicated that the higher incidence of UTI is likely due to the higher frequency of urinary retention observed among Ona A–treated patients, which would predispose patients to infection. Further, the higher incidence of urinary retention in the Ona A groups likely explained the higher incidence of CIC in the Ona A groups. It should be noted that the use of Ona A in bladder dysfunction is contraindicated in patients who are not willing and able to have CIC initiated, which may reduce the number of patients with OAB with an inadequate response or intolerance to anticholinergic medications who are appropriate candidates for Ona A. However, the clinical expert suggested that patients can accept indwelling catheterization for the duration of retention as an alternative to CIC.

No increased risk of cardiac events or anaphylaxis or hypersensitivity reactions was observed for Ona A compared with placebo. Limited data on adverse events were reported for P030438 study. Long-term harms data for the approved dose of Ona A in OAB are relatively limited, with the majority of randomized controlled comparative harms data restricted to 12 weeks. Bearing in mind the limitations of the open-label extension study (see APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY), there do not appear to be any new safety signals from the extension trial data.

5. CONCLUSIONS

Two phase 3 and two phase 2 placebo-controlled studies compared Ona A with placebo in adult patients with symptoms of idiopathic overactive bladder that had not been adequately managed with anticholinergic therapies. In the phase 3 studies (095 and 520), compared with placebo, Ona A resulted in statistically significantly greater reductions from baseline in incontinence episodes, urge-incontinence episodes, urgency episodes, micturitions, and nocturia episodes. There is no generally recognized standard for the change or the difference in change for these outcomes to be judged clinically significant. However, the clinical expert consulted for this review considered the observed differences to be of clinical importance. In addition, studies 095 and 520 reported statistically significant and clinically important improvements in disease-specific health-related quality of life measures (KHQ and I-QOL) for patients treated with Ona A versus placebo. In the phase 2 studies (077 and P030438), there was no statistically significant difference between Ona A and placebo in terms of urge incontinence frequency.

The proportion of patients who experienced adverse events, serious adverse events, and withdrawals due to adverse events was higher in the Ona A groups. Overall, the most frequent adverse events associated with Ona A were UTI, dysuria, urinary retention, bacteriuria, increased residual urine volume, and use of CIC for urinary retention. No increased risk of cardiac events or anaphylaxis or hypersensitivity reactions was observed for Ona A compared with placebo.

The trials, which assessed only a single dose, are limited by the lack of an active comparator and their short duration.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Continence Foundation (TCCF; formerly The Simon Foundation for Continence Canada) is the only national non-profit organization serving the interests of people experiencing incontinence. The mission of the TCCF is to enhance the quality of life for people experiencing incontinence by providing education and information about incontinence and available treatment options. TCCF is funded by donations from the public, health care professionals, and industry; specific industry donors include Allergan, Astellas, LABORIE, and the TENA brand by SCA. TCCF has declared no conflict of interest with respect to the compilation of this submission.

2. Condition and Current Therapy-Related Information

Information for this submission was compiled by TCCF primarily through a cross-sectional survey of a random cohort of Canadian patients with overactive bladder (OAB) currently receiving treatment who were initially identified from the TCCF database. One hundred patients were recruited and 76 completed the survey. Of those who responded, a majority of patients indicated having symptoms of urinary urgency (82%) and urge incontinence (82%), while more than half reported increased urinary frequency (58%), and nocturia (55%). The table below presents the day-to-day problems reported by patients with OAB and the improvements they would like to see.

Survey Feedback from Patients With Overactive Bladder	
Day-to-day problems reported:	**Desired changes in day-to-day life reported:**
• Inability to leave home as often as desired, including not going on holiday	• Reduction in daily or weekly incontinence episodes
• Having to "toilet-map" route before leaving home	• Reduction in urinary frequency, especially nocturia episodes
• Avoiding public transport	• No need for incontinence pads or diapers
• Reduction in sexual activity and avoidance of new intimate relationships	• Control over when and where urination takes place when not at home
• Fear of odour	• Not having to limit social activities because of fear of having an "accident"
• Reduced ability to work or loss of productivity	• Affordable absorbent products and incontinence care
• Interrupted sleep due to toilet visits	
• Financial burden from purchasing incontinence supplies	

According to TCCF, nearly 10% of Canadians (3.3 million people) experience some form of urinary incontinence (UI). In a recent epidemiologic survey conducted by TCCF, UI was reported in 36% of community-dwelling women. UI is described as an embarrassing and debilitating symptom associated with reduced quality of life and increased economic burden. Because of the social stigma of the condition, those afflicted often suffer in silence without seeking medical care.

Two-thirds of surveyed patients reported taking anticholinergic medications for OAB, with almost half reporting varying levels of efficacy and the other one-third using behavioural treatment. While anticholinergic drugs are considered the mainstay of treatment, they are often discontinued due to poor tolerability (e.g., dry mouth, constipation, blurred vision, being unable to drive, cognitive impairment) or incomplete response to treatment. Patients with OAB may need to get up frequently at night to urinate, thus placing them at increased risk for reduced sleep quality, as well as falls and fractures (particularly among the elderly). Falls and incontinence are cited as two of the four leading causes for placement in long-term care facilities in Canada.

Despite treatment, patients with OAB still report having to make stops at a washroom en route to work, persistent fears about urine leakage (or losing complete control) when going from a seated to standing position, and dealing with the associated feelings of embarrassment, reduced self-esteem, and a sense of loss of control over one's life.

The cost of absorbent products is considerable and no subsidies are available for these.

Caregivers of patients with OAB also reported being negatively affected, whether it be through having to assist with changes in absorbent products, keeping up with laundering or cleaning needs, or ensuring that their loved one gets to the toilet on time, including during the night.

3. Related Information About the Drug Being Reviewed

Information for this section was gathered through interviews with patients who had previously had Botox treatment for OAB, as well as from experience gathered over the years by TCCF.

Patients with OAB receiving treatment expected that a new drug would control their symptoms more effectively, have a lower risk of side effects than current treatments, improve their quality of life (including reducing their anxiety about urine leakage), improve their sleep quality, and be easier to take.

Among the surveyed patients, those who had some experience with Botox treatment described how this therapy had improved their quality of life. Comments centred on reductions in urinary frequency and urine leakage, and the sense of freedom that came from not having to wear bulky absorbent products or to toilet-map. Concerns about access to and affordability (e.g., reimbursement) of Botox were also raised.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 29, 2014
Alerts:	Weekly search updates until October 17, 2014
Study Types:	Randomized controlled trials
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line	**Strategy**
1	exp Botulinum Toxin Type A/
2	(botulinum* or botox or dysport* or oculinum or BTX-A or BTX*or BtA or BoNTA* or BoNT A or Botulin A or Botulin toxin A or Neuronox or Onaclostox or Xeomin or nabotulinumtoxinA or onabotulinum*).ti,ab,ot,sh,hw,rn,nm.
3	(93384-43-1 or EC 3-4-24-69).rn,nm.
4	1 or 2 or 3
5	exp Urinary Bladder, Overactive/ or exp Urinary Incontinence/ or exp Urinary Bladder, Neurogenic/
6	(Detrusor* or intradetrusor* or intra detrusor* or urge syndrome*).ti,ab,ot,sh,hw.
7	((Bladder* or urinary or urination or voiding) adj3 (incontinence or overactive or overactivity or neurogenic)).ti,ab,ot,sh,hw.
8	5 or 6 or 7
9	4 and 8
10	9 use pmez
11	exp *botulinum toxin A/
12	(botulinum* or botox or dysport* or oculinum or BTX* or BTX-A or BtA or BoNTA* or BoNT A or Botulin A or Botulin toxin A or Neuronox or Onaclostox or Xeomin or nabotulinumtoxinA or onabotulinum*).ti,ab.
13	11 or 12
14	exp urinary urgency/ or exp urine incontinence/ or exp urge incontinence/ or exp overactive bladder/
15	(Detrusor* or intradetrusor* or intra detrusor* or urge syndrome*).ti,ab.
16	((Bladder* or urinary or urination or voiding) adj3 (incontinence or overactive or overactivity or neurogenic)).ti,ab.
17	14 or 15 or 16
18	13 and 17
19	18 use oemezd
20	10 or 19
21	20 not conference abstract.pt.
22	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
23	Randomized Controlled Trial/
24	Randomized Controlled Trials as Topic/
25	"Randomized Controlled Trial (topic)"/
26	Controlled Clinical Trial/
27	Controlled Clinical Trials as Topic/
28	"Controlled Clinical Trial (topic)"/
29	Randomization/
30	Random Allocation/
31	Double-Blind Method/
32	Double Blind Procedure/
33	Double-Blind Studies/
34	Single-Blind Method/
35	Single Blind Procedure/
36	Single-Blind Studies/

MULTI-DATABASE STRATEGY	
Line	**Strategy**
37	Placebos/
38	Placebo/
39	Control Groups/
40	Control Group/
41	(random* or sham or placebo*).ti,ab,hw.
42	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
43	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
44	(control* adj3 (study or studies or trial*)).ti,ab.
45	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
46	allocated.ti,ab,hw.
47	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
48	or/22-47
49	21 and 48
50	remove duplicates from 49

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	To December May 29, 2014
Keywords:	Botox, onabotulinumtoxin A, botulinumtoxin A, Dysport, Nurobloc, incontinence, incontinent, OAB, bladder, overactive, overactivity
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Brubaker et al., 2012[37]	Outcome not of interest
Flynn et al., 2014[38]	Inappropriate dose
Wein 2013[39]	Editorial comment
Shirvan et al., 2013 [40]	Inappropriate intervention
Visco et al., 2012 [41]	Inappropriate intervention
Visco et al., 2012 [42]	Inappropriate intervention
Jabs and Carleton 2013 [43]	Inappropriate intervention

APPENDIX 4: DETAILED OUTCOME DATA

Bladder Activity: Micturition Episodes

TABLE 8: MICTURITION EPISODES

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Mean daily frequency of micturition episodes		
Study 191622-095[ab]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	11.98 (4.3)	11.20 (3.1)
Week 12, n	263	258
Change from baseline at week 12, LS mean (95% CI)	−2.01 (−2.39 to −1.64)	−0.98 (−1.34 to −0.61)
LS mean difference (95% CI), *P* value versus placebo at week 12	−1.04 (−1.48 to −0.59) *P* < 0.001	ref
Study 191622-520[ab]	**N = 277**	**N = 271**
Baseline, n	277	270
Baseline, mean (SD)	12.01 (4.0)	11.77 (3.6)
Week 12, n	264	260
Change from baseline at week 12, LS mean (95% CI)	−2.35 (−2.74 to −1.96)	−0.63 (−1.04 to −0.22)
LS mean difference (95% CI), *P* value versus placebo at week 12	−1.72 (−2.19 to −1.26) *P* < 0.001	ref
Study P030438	**N = 22**	**N = 29**
P values of MD at 90 days versus placebo	*P* < 0.001	ref
P values of MD at 180 days versus placebo	NS	ref
Mean weekly frequency of micturition episodes		
Study 191622-077[a]	**N = 54**	**N = 44**
Baseline, n	54	44
Baseline, mean (SD)	80.3 (22.6)	73.3 (23.0)
Week 12, n	48	39
Mean change from baseline at week 12 (SD)	−21.7 (19.8)	−8.3 (22.9)
MD (95% CI), *P* value versus placebo at week 12[c]	−8.2 (−16.5 to 0.12) *P* = 0.053	ref
Week 36, n	44	35
Mean change from baseline at week 36 (SD)	−22.9 (17.5)	−9.3 (26.5)
MD (95% CI), *P* value versus placebo at week 36[c]	−8.2 (−16.4 to 0.0) *P* = 0.050	ref

CI = confidence interval; LS = least squares; MD = mean difference; NS = not statistically significant; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.

[a] Intention-to-treat population; missing values were not imputed.

[b] *P* values for between-treatment comparisons are from an analysis of covariance model with treatment group as factor, baseline value of micturition episodes, stratification factor and site as covariates.

[c] *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline as a covariate.

Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report;[21] Study 191622-077 Clinical Study Report;[22] Denys et al.[19]

Bladder Activity: Incontinence Episodes

TABLE 9: INCONTINENCE EPISODES

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Mean daily frequency of incontinence episodes		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, mean (SD)	5.47 (3.6)	5.09 (3.2)
Change from baseline at week 12, LS mean (95% CI)	−2.52 (−2.91 to −2.12)	−0.87 (−1.25 to −0.48)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.65 (−2.13 to −1.17) *P* < 0.001	ref
Percentage of patients with ≥ 50% reduction in incontinence episodes at week 12	57.5%	28.9%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with ≥ 75% reduction in incontinence episodes at week 12	44.6%	15.2%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with 100% reduction in incontinence episodes at week 12	22.9%	6.5%
P value compared with placebo[c]	*P* < 0.001	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, mean (SD)	5.52 (3.8)	5.70 (3.9)
Change from baseline at week 12, LS mean (95% CI)	−2.96 (−3.40 to −2.53)	−1.05 (−1.50 to −0.60)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.91 (−2.43 to −1.39) *P* < 0.001	ref
Percentage of patients with ≥ 50% reduction in incontinence episodes at week 12	63.5%	33.2%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with ≥ 75% reduction in incontinence episodes at week 12	47.3%	20.3%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with 100% reduction in incontinence episodes at week 12	31.4%	10.3%
P value compared with placebo[c]	*P* < 0.001	ref
Study 191622-077	NR	NR
Study P030438	NR	NR

CI = confidence interval; LS = least squares; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.

[a] Intention-to-treat population; missing values were imputed using last observation carried forward method.

[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of urinary-incontinence episodes, and site as covariates.

[c] *P* values for between-treatment comparisons are based on Cochran–Mantel–Haenszel test with urinary urgency incontinence ≤ 9 or > 9 episodes at baseline as a stratification factor.

Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report.[21]

TABLE 10: SUBGROUP ANALYSIS OF INCONTINENCE EPISODES BY AGE

Study	Age < 65 years		Age ≥ 65 years	
	Treatment		Treatment	
Outcome	Ona A 100 U	Placebo	Ona A 100 U	Placebo
Mean daily frequency of incontinence episodes				
Study 191622-095[a]	**N = 159**	**N = 160**	**N = 121**	**N = 117**
Baseline, mean (SD)	5.06 (3.4)	4.86 (3.2)	6.0 (3.8)	5.4 (3.2)
Change from baseline at week 12, LS mean (95% CI)	−2.38 (−2.93 to −1.82)	−0.97 (−1.50 to −0.44)	−2.40 (−2.95 to −1.85)	−0.96 (−1.51 to −0.41)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.40 (−2.09 to −0.72) *P* < 0.001	ref	−1.44 (−2.19 to −0.69) *P* < 0.001	ref
Study 191622-520[a]	**N = 153**	**N = 163**	**N = 124**	**N = 108**
Baseline, mean (SD)	4.9 (3.3)	5.1 (3.6)	6.3 (4.1)	6.5 (4.1)
Change from baseline at week 12, LS mean (95% CI)	−2.50 (−3.06 to −1.94)	−0.83 (−1.37 to −0.29)	−3.46 (−4.18 to −2.74)	−1.37 (−2.19 to −0.55)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.67 (−2.34 to −1.00) *P* < 0.001	ref	−2.09 (−3.10 to −1.09) *P* < 0.001	ref
Study 191622-077	NR	NR	NR	NR
Study P030438	NR	NR	NR	NR

CI = confidence interval; LS = least squares; NR = not reported; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.

[a] Intention-to-treat population; missing values were imputed using last observation carried forward method.

[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of urinary-incontinence episodes and site as covariates.

Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report.[21]

Bladder Activity: Urge-Incontinence Episodes

TABLE 11: URGE-INCONTINENCE EPISODES

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Mean daily frequency of urge-incontinence episodes		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	4.8 (3.2)	4.5 (3.1)
Week 12, n	263	258
Change from baseline at week 12, LS mean (95% CI)	−2.35 (−2.8 to −2.0)	−0.69 (−1.1 to −0.3)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.66 (−2.1 to −1.2) *P* < 0.001	ref
Percentage of patients with ≥ 50% reduction in urge-incontinence episodes at week 12	61.2%	29.1%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with ≥ 75% reduction in urge-incontinence episodes at week 12	48.3%	15.5%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with 100% reduction in urge-incontinence episodes at week 12	28.9%	7.8%
P value compared with placebo[c]	*P* < 0.001	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	277	271
Baseline, mean (SD)	5.1 (3.7)	5.2 (3.7)
Week 12, n	264	260
Change from baseline at week 12, LS mean (95% CI)	−2.82 (−3.4 to −2.4)	−0.85 (−2.1 to −0.7)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.97 (−2.5 to −1.5) *P* < 0.001	ref
Percentage of patients with ≥ 50% reduction in urge-incontinence episodes at week 12	64.8%	31.5%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with ≥ 75% reduction in urge-incontinence episodes at week 12	48.1%	20.8%
P value compared with placebo[c]	*P* < 0.001	ref
Percentage of patients with 100% reduction in urge-incontinence episodes at week 12	31.8%	13.1%
P value compared with placebo[c]	*P* < 0.001	ref
Study P030438[d]	**N = 20**	**N = 28**
Percentage of patients with ≥ 50% improvement in urgency and urge-incontinence episodes at month 3	65%	29%
P value compared with placebo	0.09	ref
Percentage of patients with ≥ 75% improvement in urgency and urge-incontinence episodes at month 3	40%	18%
P value compared with placebo	0.06	ref
Mean weekly frequency of urinary urge-incontinence episodes		
Study 191622-077[e]	**N = 54**	**N = 44**
Baseline, mean (SD)	27.8 (22.7)	32.5 (20.2)
Mean change from baseline at week 12 (SD)	−18.4 (20.2)	−17.4 (18.2)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
MD at week 12[f]	−4.8 (−10.4 to 0.8) *P* = 0.094	ref
Mean change from baseline at week 36 (SD)	−18.5 (18.2)	−17.9 (17.7)
MD at week 36[f]	−4.7 (−10.0 to 0.7) *P* = 0.085	ref
Percentage of patients with ≥ 50% reduction in urge-incontinence episodes at week 12	70.4%	52.3%
P value compared with placebo[g]	*P* = 0.07	ref
Percentage of patients with ≥ 50% reduction in urge-incontinence episodes at week 36	66.7%	45.5%
P value compared with placebo[g]	*P* = 0.04	ref
Percentage of patients with ≥ 75% reduction in urge-incontinence episodes at week 12	55.6%	36.4%
P value compared with placebo[g]	*P* = 0.06	ref
Percentage of patients with ≥ 75% reduction in urge-incontinence episodes at week 36	50.0%	27.3%
P value compared with placebo[g]	*P* = 0.02	ref
Percentage of patients with 100% reduction in urge-incontinence episodes at week 12	37.0%	15.9%
P value compared with placebo[g]	*P* = 0.02	ref
Percentage of patients with 100% reduction in urge-incontinence episodes at week 36	33.3%	11.4%
P value compared with placebo[g]	*P* = 0.01	ref

CI = confidence interval; LS = least squares; MD = mean difference; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.

[a] Intention-to-treat population; missing values were not imputed.

[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of urinary urge-incontinence episodes and site as covariates.

[C] *P* values for between-treatment comparisons are based on Cochran–Mantel–Haenszel test with urinary urge-incontinence ≤ 9 or > 9 episodes at baseline as a stratification factor.

[d] Results include both urgency and urge urinary incontinence, calculated with the last observation carried forward.

[e] Intention-to-treat population; missing values were imputed using last observation carried forward method.

[f] *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline as a covariate.

[g] Calculated by CADTH using Review Manager.

Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report;[21] Study 191622-077 Clinical Study Report;[22] Denys et al.[19]

Bladder Activity: Nocturia Episodes

TABLE 12: NOCTURIA EPISODES

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Mean daily frequency of nocturia episodes		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	2.15 (1.5)	2.01 (1.3)
Week 12, n	263	258
Change from baseline at week 12, LS mean (95% CI)	−0.45 (−0.60 to −0.30)	−0.25 (−0.40 to −0.10)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−0.20 (−0.38 to −0.02) *P* = 0.029	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	277	270
Baseline, mean (SD)	2.19 (1.5)	2.08 (1.5)
Week 12, n	264	260
Change from baseline at week 12, LS mean (95% CI)	−0.46 (−0.69 to −0.31)	−0.18 (−0.60 to 0.05)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−0.27 (−0.47 to −0.08) *P* = 0.007	ref
Mean weekly frequency of nocturia episodes		
Study 191622-077[a]	**N = 54**	**N = 44**
Baseline, n	54	44
Baseline, mean (SD)	13.9 (6.9)	12.3 (8.2)
Week 12, n	48	39
mean change from baseline at week 12 (SD)	−4.1 (7.0)	−0.3 (6.8)
MD (95% CI), *P* value versus placebo at week 12[c]	−2.1 (−5.0 to 0.87) *P* = 0.166	ref
Week 36, n	44	35
mean change from baseline at week 36 (SD)	−4.1 (4.4)	0.5 (9.2)
MD (95% CI), *P* value versus placebo at week 36[c]	−2.3 (−5.6 to 1.0) *P* = 0.172	ref
Study P030438	NA	NA

CI = confidence interval; LS = least squares; MD = mean difference; NA = not applicable;
Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.
[a] Intention-to-treat population; missing values were not imputed.
[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of nocturia episodes, and sites as covariates.
[c] *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline as a covariate.
Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report;[21] Study 191622-077 Clinical Study Report.[22]

Bladder Activity: Urgency Episodes

TABLE 13: URGENCY EPISODES

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Mean daily frequency of urgency episodes		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	8.54 (4.7)	7.85 (3.7)
Week 12, n	263	258
Change from baseline at week 12, LS mean (95% CI)	−2.76 (−3.30 to −2.23)	−1.26 (−1.78 to −0.73)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.51 (−2.15 to −0.87) *P* < 0.001	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	277	270
Baseline, mean (SD)	9.11 (4.6)	8.78 (4.5)
Week 12, n	264	260
Change from baseline at week 12, LS mean (95% CI)	−3.39 (−3.93 to −2.84)	−0.95 (−1.52 to −0.37)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−2.44 (−3.09 to −1.79) *P* < 0.001	ref
Study P030438	**N = 22**	**N = 29**
P values of MD at 90 days versus placebo	NS	ref
P values of MD at 180 days versus placebo	NS	ref
Mean weekly frequency of urgency episodes		
Study 191622-077[a]	**N = 54**	**N = 44**
Baseline, n	54	44
Baseline, mean (SD)	69.9 (28.2)	62.0 (26.6)
Week 12, n	48	39
Mean change from baseline at week 12 (SD)	−30.5 (27.6)	−14.1 (30.2)
MD (95% CI), *P* value versus placebo at week 12[c]	−11.7 (−23.0 to −0.4) *P* = 0.043	ref
Week 36, n	44	35
Mean change from baseline at week 36 (SD)	−30.1 (24.9)	−15.1 (32.9)
MD (95% CI), *P* value versus placebo at week 36[c]	−9.1 (−20.2 to 2.0) *P* = 0.109	ref

CI = confidence interval; LS = least squares; MD = mean difference; NS = not statistically significant; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.

[a] Intention-to-treat population; missing values were not imputed.

[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of urgency episodes, stratification factor, and site as covariates.

[c] *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline as a covariate.

Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report;[21] Study 191622-077 Clinical Study Report;[22] Denys et al.[19]

Bladder Activity: Time to Request and Qualify for Re-treatment

TABLE 14: TIME TO REQUEST AND QUALIFY FOR RE-TREATMENT AND PROPORTION OF PATIENTS WHO REQUESTED RE-TREATMENT

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Study 191622-095	**N = 280**	**N = 277**
Patients who requested re-treatment, n (%)	173 (61.8)	223 (80.5)
Time to request for re-treatment		
Median (weeks)	21.1	12.4
95% CI for median (weeks)	(18.3 to 24.0)	(12.3 to 13.0)
P value versus placebo[a]	*P* < 0.001	ref
Patients who received re-treatment, n (%)	150 (53.6)	222 (80.1)
Time to request for re-treatment		
Median (weeks)	24	12.6
95% CI for median (weeks)	(20.4 to 25.1)	(12.3 to 13.1)
P value versus placebo[a]	*P* < 0.001	ref
Study 191622-520	**N = 277**	**N = 271**
Patients who requested re-treatment, n (%)	175 (63.2)	229 (84.5)
Time to request for re-treatment		
Median (weeks)	18.1	12.9
95% CI for median (weeks)	(17.4 to 22.9)	(12.4 to 13.1)
P value versus placebo[a]	*P* < 0.001	ref
Patients who received re-treatment, n (%)	170 (61.4)	227 (83.8)
Time to request for re-treatment		
Median (weeks)	19.1	13.1
95% CI for median (weeks)	(18.1 to 24)	(12.6 to 13.3)
P value versus placebo[a]	*P* < 0.001	ref
Study 191622-077	NA	NA
Study P030438	NA	NA

CI = confidence interval; NA = not applicable; Ona A = onabotulinumtoxinA; ref = reference group.
[a] *P* value is from stratified log-rank test with baseline urinary urge-incontinence episodes as stratification factor.
Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report.[21]

Health-Related Quality of Life Data

TABLE 15: HEALTH-RELATED QUALITY OF LIFE OUTCOMES (KING'S HEALTH QUESTIONNAIRE)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
KHQ — General Health Perception		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	22.8 (19.1)	23.4 (17.4)
Week 12, n	263	254
Change from baseline at week 12, LS mean	0.9 (−1.3 to 3.1)	2.3 (0.2 to 4.5)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−1.5 (−4.1 to 1.1) *P* = 0.271	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	39.8 (24.9)	41.3 (26.2)
Week 12, n	262	255
Change from baseline at week 12, LS mean	−5.4 (−8.2 to −2.7)	−0.4 (−3.3 to 2.4)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−5.0 (−8.3 to −1.7) *P* = 0.003	ref
KHQ — Incontinence Impact		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	81.1 (25.5)	81.3 (24.1)
Week 12, n	263	254
Change from baseline at week 12, LS mean	−18.8 (−23.2 to −14.5)	−3.4 (−7.6 to 0.9)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−15.5 (−20.6 to −10.4) *P* < 0.001	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	85.6 (23.6)	85.6 (21.9)
Week 12, n	262	255
Change from baseline at week 12, LS mean (95% CI)	−23.4 (−27.6 to −19.2)	−8.5 (−12.9 to −4.2)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−14.9 (−19.9 to −9.9) *P* < 0.001	ref
KHQ — Role Limitations		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	61.2 (30.4)	56.2 (30.1)
Week 12, n	264	254
Change from baseline at week 12, LS mean (95% CI)	−22.1 (−26.3 to −17.9)	−1.4 (−5.5 to 2.7)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−20.64 (−25.56 to −15.73) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	69.6 (26.8)	66.4 (26.8)
Week 12, n	262	256

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Change from baseline at week 12, LS mean (95% CI)	−26.4 (−30.6 to −22.1)	−6.6 (−11.0 to −2.2)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−19.8 (−24.8 to −14.7) *P* < 0.001	ref
KHQ — Social Limitations		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	40.5 (30.7)	39.4 (30.1)
Week 12, n	264	254
Change from baseline at week 12, LS mean (95% CI)	−15.8 (−19.4 to −12.2)	−1.9 (−5.4 to 1.6)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−13.89 (−18.07 to −9.71) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	49.1 (31.5)	45.4 (30.8)
Week 12, n	262	256
Change from baseline at week 12, LS mean (95% CI)	−16.2 (−20.0 to −12.3)	−3.0 (−7.0 to 1.0)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−13.2 (−17.8 to −8.6) *P* < 0.001	ref
KHQ — Physical Limitations		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	63.5 (29.3)	60.3 (31.8)
Week 12, n	264	254
Change from baseline at week 12, LS mean (95% CI)	−20.0 (−24.4 to −15.6)	−5.1 (−9.4 to −0.8)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−14.9 (−20.1 to −9.8) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	70.5 (27.2)	69.5 (27.1)
Week 12, n	262	256
Change from baseline at week 12, LS mean (95% CI)	−22.2 (−26.4 to −18.1)	−6.3 (−10.6 to −2.0)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−15.9 (−20.9 to −10.9) *P* < 0.001	ref
KHQ — Personal Relationship		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	203	215
Baseline, mean (SD)	35.0 (34.9)	33.7 (35.2)
Week 12, n	165	190
Change from baseline at week 12, LS mean (95% CI)	−11.2 (−15.6 to −6.8)	1.9 (−2.2 to 6.0)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−13.1 (−18.4 to −7.7) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	214	202
Baseline, mean (SD)	40.7 (36.0)	38.8 (36.5)
Week 12, n	184	171
Change from baseline at week 12, LS mean (95% CI)	−10.2 (−14.8 to −5.5)	−0.8 (−5.7 to 4.0)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−9.3 (−15.0 to −3.7) *P* = 0.001	ref
KHQ — Emotions		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	49.8 (31.5)	49.9 (29.2)
Week 12, n	264	254
Change from baseline at week 12, LS mean (95% CI)	−16.0 (−19.6 to −12.4)	−3.4 (−6.9 to 0.1)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−12.6 (−16.8 to −8.4) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	62.4 (29.9)	60.8 (28.4)
Week 12, n	262	256
Change from baseline at week 12, LS mean (95% CI)	−19.4 (−23.1 to −15.6)	−4.2 (−8.1 to −0.3)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−15.2 (−19.6 to −10.7) *P* < 0.001	ref
KHQ — Sleep and Energy		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	64.6 (26.1)	65.6 (26.6)
Week 12, n	264	254
Change from baseline at week 12, LS mean (95% CI)	−12.7 (−16.2 to −9.2)	−2.2 (−5.6 to 1.2)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−10.5 (−14.5 to −6.4) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	64.8 (27.9)	64.9 (26.6)
Week 12, n	262	256
Change from baseline at week 12, LS mean (95% CI)	−19.1 (−22.3 to −15.8)	−5.8 (−9.2 to −2.4)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−13.2 (−17.2 to −9.3) *P* < 0.001	ref
KHQ — Severity Coping Measure		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	64.9 (22.5)	62.7 (23.0)
Week 12, n	264	254
Change from baseline at week 12, LS mean (95% CI)	−18.5 (−21.7 to −15.3)	−2.4 (−5.6 to 0.7)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−16.0 (−19.8 to −12.3) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	66.4 (23.2)	66.5 (23.1)
Week 12, n	262	256
Change from baseline at week 12, LS mean (95% CI)	−19.9 (−23.0 to −16.8)	−3.9 (−7.1 to −0.7)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	−16.0 (−19.7 to −12.3) *P* < 0.001	ref
KHQ — Utility Score		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	278	276
Baseline, mean (SD)	0.93 (0.024)	0.93 (0.023)
Week 12, n	264	254
Change from baseline at week 12, LS mean (95% CI)	0.02 (0.01 to 0.02)	0.00 (−0.00 to 0.00)
LS mean difference (95% CI), *P* value versus placebo at week 12[d]	0.0 (0.0 to 0.0) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	270
Baseline, mean (SD)	0.92 (0.023)	0.93 (0.021)
Week 12, n	262	256
Change from baseline at week 12, LS mean (95% CI)	0.02 (0.02 to 0.02)	0.01 (0.00 to 0.01)
LS mean difference (95% CI), *P* value versus placebo at week 12[d]	0.01 (0.01 to 0.02) *P* < 0.001	ref
KHQ — Symptoms Component		
Study 191622-077[c]	**N = 54**	**N = 44**
Baseline, n	54	43
Baseline, mean (SD)	45.3 (14.1)	42.1 (11.7)
Week 12, n	47	36
Mean change from baseline at week 12 (SD)	−18.1 (18.0)	−9.3 (17.7)
MD (95% CI), *P* value versus placebo at week 12[e]	−9.0 (−15.8 to −2.3) *P* = 0.009	ref
Week 36, n	44	36
Mean change from baseline at week 36 (SD)	−11.0 (16.8)	−8.7 (16.5)
MD (95% CI), *P* value versus placebo at week 36[e]	−3.0 (−9.6 to 3.7) *P* = 0.379	ref

CI = confidence interval; KHQ = King's Health Questionnaire; LS = least squares; MD = mean difference; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.

[a] Intention-to-treat population; missing values were not imputed.

[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of domain score, stratification factor, and site as covariates.

[c] Intention-to-treat population; missing values were imputed if at least half of the items in the domain had non-missing responses.

[d] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of utility score, stratification factor, and site as covariates.

[e] *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline as a covariate.

Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report;[21] Study 191622-077 Clinical Study Report.[22]

TABLE 16: HEALTH-RELATED QUALITY OF LIFE OUTCOMES (INCONTINENCE QUALITY OF LIFE QUESTIONNAIRE)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
I-QOL Total Summary Score		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	36.5 (20.6)	37.3 (19.4)
Week 12, n	266	255
Change from baseline at week 12, LS mean (95% CI)	19.8 (16.6 to 23.0)	4.9 (1.7 to 8.1)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	14.92 (11.13 to 18.71) *P* < 0.001	ref
Study 191622-520	**N = 277**	**N = 271**
Baseline, n	274	270
Baseline, mean (SD)	31.7 (17.0)	32.1 (17.2)
Week 12, n	261	254
Change from baseline at week 12, LS mean (95% CI)	22.8 (19.8 to 25.9)	5.9 (2.7 to 9.1)
LS mean difference (95% CI), *P* value versus placebo at week 12 [b]	16.9 (13.2 to 20.6) *P* < 0.001	ref
Study 191622-077[a]	**N = 54**	**N = 44**
Baseline, n	54	44
Baseline, mean (SD)	34.3 (17.8)	35.9 (19.8)
Week 12, n	46	38
Mean change from baseline at week 12 (SD)	32.9 (25.7)	17.9 (25.5)
MD (95% CI), *P* value versus placebo at week 12[e]	14.8 (5.3 to 24.4) *P* = 0.002	ref
Week 36, n	47	37
Mean change from baseline at week 36 (SD)	27.7 (24.8)	12.3 (25.3)
MD (95% CI), *P* value versus placebo at week 36[e]	15.2 (4.6 to 25.7) *P* = 0.005	ref
Study P030438	**N = 22**	**N = 29**
P values of MD at 90 days versus placebo	0.01 ≤ *P* < 0.05	ref
P values of MD at 180 days versus placebo	0.001 ≤ *P* < 0.05	ref
I-QOL Avoidance and Limiting Behaviour		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	31.9 (18.22)	31.9 (17.4)
Week 12, n	266	255
Change from baseline at week 12, LS mean (95% CI)	22.2 (18.7 to 25.6)	5.2 (1.9 to 8.6)
LS mean difference (95% CI), *P* value versus placebo at week 12[d]	16.9 (12.9 to 21.0) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	271
Baseline, mean (SD)	30.6 (15.9)	31.4 (16.4)
Week 12, n	262	257
Change from baseline at week 12, LS mean (95% CI)	23.1 (20.0 to 26.1)	5.4 (2.2 to 8.5)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
LS mean difference (95% CI), *P* value versus placebo at week 12[d]	17.7 (14.0 to 21.4) *P* < 0.001	ref
Study 191622-077[c]	**N = 54**	**N = 44**
Baseline, n	54	44
Baseline, mean (SD)	30.6 (15.1)	32.0 (17.3)
Week 12, n	48	38
Mean change from baseline at week 12 (SD)	34.7 (26.4)	19.3 (26.7)
MD (95% CI), *P* value versus placebo at week 12[e]	15.8 (5.8 to 25.9) *P* = 0.002	ref
Week 36, n	47	37
Mean change from baseline at week 36 (SD)	28.9 (26.7)	13.0 (24.7)
MD (95% CI); *P* value versus placebo at week 36[e]	17.2 (6.3 to 28.1) *P* = 0.002	ref
Study P030438	**N = 22**	**N = 29**
P values of MD at 90 days versus placebo	0.01 ≤ *P* < 0.05	ref
P values of MD at 180 days versus placebo	0.01 ≤ *P* < 0.05	ref
I-QOL Psychosocial Impact		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	46.6 (26.06)	47.6 (24.18)
Week 12, n	266	255
Change from baseline at week 12, LS mean (95% CI)	17.4 (14.2 to 20.6)	4.1 (1.0 to 7.2)
LS mean difference (95% CI), *P* value versus placebo at week 12[d]	13.3 (9.6 to 17.0) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	271
Baseline, mean (SD)	37.9 (22.7)	38.2 (22.4)
Week 12, n	262	257
Change from baseline at week 12, LS mean (95% CI)	21.0 (17.8 to 24.2)	5.8 (2.5 to 9.1)
LS mean difference (95% CI); *P* value versus placebo at week 12[d]	15.2 (11.3 to 19.0) *P* < 0.001	ref
Study 191622-077[c]	**N = 54**	**N = 44**
Baseline, n	54	44
Baseline, mean (SD)	42.3 (23.3)	45.2 (26.2)
Week 12, n	48	38
Mean change from baseline at week 12 (SD)	29.5 (23.9)	14.5 (25.2)
MD (95% CI), *P* value versus placebo at week 12[e]	14.6 (5.5 to 23.7) *P* = 0.002	ref
Week 36, n	47	37
Mean change from baseline at week 36 (SD)	25.3 (25.6)	10.8 (28.4)
MD (95% CI), *P* value versus placebo at week 36[e]	12.2 (1.5 to 22.9) *P* = 0.026	ref
Study P030438	**N = 22**	**N = 29**
P values of MD at 90 days versus placebo	0.01 ≤ *P* < 0.05	ref
P values of MD at 180 days versus placebo	0.001 ≤ *P* < 0.05	ref

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
I-QOL Social Embarrassment		
Study 191622-095[c]	**N = 280**	**N = 277**
Baseline, n	280	277
Baseline, mean (SD)	25.7 (21.99)	27.6 (21.87)
Week 12, n	266	255
Change from baseline at week 12, LS mean (95% CI)	20.6 (16.9 to 24.3)	5.7 (2.1 to 9.3)
LS mean difference (95% CI), *P* value versus placebo at week 12[d]	14.9 (10.6 to 19.2) *P* < 0.001	ref
Study 191622-520[c]	**N = 277**	**N = 271**
Baseline, n	275	271
Baseline, mean (SD)	23.0 (19.5)	22.4 (19.9)
Week 12, n	262	257
Change from baseline at week 12, LS mean (95% CI)	25.4 (21.9 to 28.8)	6.2 (2.6 to 9.7)
LS mean difference (95% CI), *P* value versus placebo at week 12[d]	19.2 (15.1 to 23.3) *P* < 0.001	ref
Study 191622-077[c]	**N = 54**	**N = 44**
Baseline, n	54	44
Baseline, mean (SD)	25.7 (21.0)	25.3 (23.0)
Week 12, n	48	38
Mean change from baseline at week 12 (SD)	36.2 (31.3)	21.8 (30.2)
MD (95% CI), *P* value versus placebo at week 12[e]	15.4 (4.6 to 26.3) *P* = 0.005	ref
Week 36, n	47	37
Mean change from baseline at week 36 (SD)	30.0 (25.5)	13.9 (26.7)
MD (95% CI), *P* value versus placebo at week 36[e]	17.1 (5.6 to 28.6) *P* = 0.004	ref
Study P030438	**N = 22**	**N = 29**
P values of MD at 90 days versus placebo	NS	ref
P values of MD at 180 days versus placebo	0.001 ≤ *P* < 0.05	ref

CI = confidence interval; I-QOL = Incontinence Quality of Life Questionnaire; LS = least squares; MD = mean difference; NS = not statistically significant; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.

[a] Intention-to-treat population; missing values were imputed if three or fewer items were missing.

[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value of I-QOL, stratification factor, and site as covariates.

[c] Intention-to-treat population; missing values were not imputed.

[d] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value, stratification factor, and site as covariates.

[e] *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline as a covariate.

Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report;[21] Study 191622-077 Clinical Study Report;[22] Denys et al.[19]

TABLE 17: HEALTH-RELATED QUALITY OF LIFE OUTCOMES (12-ITEM SHORT-FORM HEALTH SURVEY)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
SF-12 Physical Component Summary score		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	280	274
Baseline, mean (SD)	44.0 (10.4)	43.7 (9.8)
week 12, n	265	251
Change from baseline at week 12, LS mean (95% CI)	1.2 (0.0 to 2.4)	0.0 (−1.2 to 1.2)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	1.2 (−0.2 to 2.6) *P* = 0.091	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	274	268
Baseline, mean (SD)	42.8 (9.9)	42.3 (9.9)
week 12, n	259	254
Change from baseline at week 12, LS mean (95% CI)	1.7 (0.6 to 2.9)	0.5 (−0.7 to 1.7)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	1.2 (−0.1 to 2.6) *P* = 0.077	ref
SF-12 Mental Component Summary Score		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	280	274
Baseline, mean (SD)	45.3 (11.7)	46.5 (11.0)
week 12, n	265	251
Change from baseline at week 12, LS mean (95% CI)	1.0 (−0.4 to 2.5)	−1.6 (−3.0 to −0.2)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	2.6 (0.9 to 4.3) *P* = 0.002	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	274	268
Baseline, mean (SD)	39.5 (11.9)	41.4 (12.0)
week 12, n	259	254
Change from baseline at week 12, LS mean (95% CI)	4.5 (3.1 to 5.8)	0.9 (−0.5 to 2.3)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	3.6 (2.0 to 5.1) *P* < 0.001	ref
SF-12 Utility Score		
Study 191622-095[a]	**N = 280**	**N = 277**
Baseline, n	280	274
Baseline, mean (SD)	0.68 (0.130)	0.69 (0.122)
week 12, n	265	251
Change from baseline at week 12, LS mean (95% CI)	0.01 (−0.00 to 0.03)	−0.01 (−0.02 to 0.01)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	0.0 (0.0 to 0.0) *P* = 0.024	ref
Study 191622-520[a]	**N = 277**	**N = 271**
Baseline, n	274	268
Baseline, mean (SD)	0.63 (0.124)	0.64 (0.124)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
week 12, n	260	254
Change from baseline at week 12, LS mean (95% CI)	0.05 (0.03 to 0.06)	0.01 (−0.00 to 0.03)
LS mean difference (95% CI), *P* value versus placebo at week 12[b]	0.04 (0.02 to 0.05) *P* < 0.001	ref
Study 191622-077	NA	NA
Study P030438	NA	NA

CI = confidence interval; LS = least squares; MD = mean difference; NA = not applicable; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation; SF-12 = 12-Item Short-Form Health Survey.
[a] Intention-to-treat population; missing values were not imputed.
[b] *P* values for between-treatment comparisons are from analysis of covariance model with treatment group as factor, baseline value, stratification factor, and site as covariates.
Source: Study 191622-520 Clinical Study Report;[20] Study 191622-095 Clinical Study Report.[21]

TABLE 18: HEALTH-RELATED QUALITY OF LIFE OUTCOMES (EQ-VAS)

Study	Treatment	
Outcome	**Ona A 100 U**	**Placebo**
Study 191622-077[a]	**N = 54**	**N = 44**
Baseline, n	53	43
Baseline, mean (SD)	71.4 (22.6)	74.3 (19.9)
Week 36, n	47	41
Mean change from baseline at week 36 (SD)	−1.7 (16.6)	−1.3 (17.1)
MD (95% CI), *P* value versus placebo at week 36[b]	2.7 (−3.6, 8.9) *P* = 0.406	ref
Study P030438	**N = 22**	**N = 29**
P values of MD at 90 days versus placebo	0.01 ≤ *P* < 0.05	ref
P values of MD at 180 days versus placebo	NS	ref

CI = confidence interval; EQ-VAS = European Quality of Life Scale Visual Analogue Scale; MD = mean difference; NS = not statistically significant; Ona A = onabotulinumtoxinA; ref = reference group; SD = standard deviation.
[a] Intention-to-treat population; missing values were not imputed.
[b] *P* values are from pairwise contrasts from an analysis of covariance model with factors for treatment group and investigator, using baseline as a covariate.
Source: Study 191622-077 Clinical Study Report;[22] Denys et al.[19]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following secondary outcome measures used in the onabotulinumtoxinA (Ona A) trials and report minimal clinically important difference (MCID) estimates where available:

- Incontinence Quality of Life questionnaire (I-QOL)
- King's Health Questionnaire (KHQ)
- 12-item Short-Form Health Survey (SF-12)
- European Quality of Life Five Dimensions Questionnaire (EQ-5D).

Findings

Incontinence Quality of Life Questionnaire

The I-QOL measure is used in patients with chronic urinary incontinence (i.e., urge, stress, and mixed) to assess the impact of incontinence on quality of life.[30,31] The I-QOL is a 22-item scale consisting of three domains: avoidance and limiting behaviour (eight items), psychosocial impacts (nine items), and social embarrassment (five items).[31] Each item is scored according to a five-point scale (1 = extremely and 5 = not at all).[28] Scores (range: 0 to 100) are calculated for each domain along with an overall composite score for the 22 items. The higher the I-QOL score, the higher the quality of life and the lower the impact of incontinence on health-related quality of life (HRQoL).[28,31] The I-QOL items have been shown to be internally consistent (overall Cronbach's alpha = 0.95, subscales: 0.87 to 0.93), with a high test–retest reliability (overall r = 0.93 after 18 days).[28] Construct validity (as demonstrated by discriminant and convergent validity) and responsiveness (e.g., ability to discriminate between perceived levels of severity) were considered acceptable.[28] The I-QOL has been translated into many languages, but only psychometrically validated in French, Spanish, Swedish, and German.[28] No MCID has been reported for non-stress incontinence, while the between-treatment MCID for the total I-QOL score in stress incontinence has been reported to be 2.5 points.[32]

King's Health Questionnaire

The standard version of the KHQ is a 21-item disease-specific questionnaire that has been developed and validated for participants with urinary incontinence.[27] The KHQ consists of nine domains: general health perceptions, impact on life, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, and incontinence severity measures. Item scores are converted to a standardized scale. Scores for each domain range from 0 to 100, where 0 indicates the best outcome or response and 100 indicates the worst outcome or response.[27]

KHQ was validated in a study of 24 patients with overactive bladder (OAB)[44] in the US, and Reese et al.[45] evaluated the psychometric properties of the KHQ in 1,284 patients with OAB. Reese et al. concluded that psychometric testing supports the reliability and validity of the KHQ as an OAB-specific measure of HRQoL.[45] Statistically significant correlations between KHQ and patient-reported OAB symptoms such as urge-incontinence episodes (median percentage change) were also observed in patients after 12 weeks of treatment with tolterodine (r = 0.16 to 0.32, $P \leq 0.0011$).[46] A within-group MCID of 5 points has been reported for each domain in patients with overactive bladder.[28,29]

Twelve-Item Short-Form Health Survey

In response to demand for a reduction in responder and research administrative burden, the SF-12, a shortened derivative of the SF-36,[33,34] was created.[47]

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[48] It consists of eight health domains: physical functioning, role — physical, bodily pain, general health, vitality, social functioning, role — emotional, and mental health.[47] For each of the eight domains, a subscale score can be calculated. The SF-36 provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS). The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population.[47]

By comparison, the SF-12 consists of 12 items from the SF-36 that are scored and weighted to obtain two summary scores: one for physical health (PCS) and one for mental health (MCS).[33,34] More than 90% of the variance in the SF-36 PCS and SF-36 MCS is captured by the items in the SF-12.[34] The SF-12 summary scores have been reported to be both psychometrically sound and good predictors of the original SF-36 scores.[33] Trading off quantity of data for increased practicality, the SF-12 is expected to be of value in studies with large sample sizes in which the objective is to survey changes in physical and mental health outcomes.[47] No published MCIDs could be found, however, for the SF-12 (or SF-36) for OAB or urinary incontinence.

European Quality of Life Five Dimensions Questionnaire

The EQ-5D is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[49,50] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged 12 years or older) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[49,50] The second part is a 20 cm visual analog scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system

(e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale have ranged from 0.033 to 0.074.[51]

In a physiotherapy study of women with urinary incontinence,[52] the EQ-5D was found to be inadequate for discriminating changes in health utility between multiple groups as a function of treatment and, thus, was not recommended by the authors for evaluating female urinary incontinence. However, in a subsequently published narrative review of the evidence (n = 17 studies; 48 to 9,487 patients per study; age of patients: 50 to 67 years) for the use of the EQ-5D in patients with urinary incontinence or complaints,[53] in which the previous study[52] was included (and criticized), the EQ-5D was found to be generally useful in the population overall, performing adequately on measures of construct validity, responsiveness, and reliability when compared with disease-specific instruments such as the I-QOL and KHQ. However, a limitation of this review was that it did not specifically examine content validity and so cannot say with certainty whether the EQ-5D adequately captures utility around incontinence indirectly through its existing dimensions.[53] No published MCIDs could be found for OAB or urinary incontinence for the EQ-5D.

TABLE 19: SUMMARY OF RELEVANT SECONDARY OUTCOMES

Instrument	Description	Validated in UI?	MCID	Comments
I-QOL	Disease-specific instrument; used in chronic UI; 22-item scale consisting of 3 domains: avoidance and limiting behaviour (8 items), psychosocial impacts (9 items), and social embarrassment (5 items). Each item scored on 5-point scale (1 = extremely and 5 = not at all). Scoring (range: 0 to 100) for each domain and overall composite score. The higher the I-QOL score, the higher the QoL.[28,30,31]	Yes[28]	Non-stress UI: unknown Stress UI: 2.5 points (total I-QOL score)[32]	Available in multiple languages.[28]
KHQ	Disease-specific instrument; used in chronic UI; 21-item scale consisting of 9 domains: general health perceptions, impact on life, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, and incontinence severity measures. Item scores converted to standardized scale. Scores range from 0 to 100, where 0 indicates best outcome or response and 100 indicates worst outcome or response.[27]	Yes[44,45]	OAB: 5 pts*[28,29]	* Only a within-group MCID reported.[28,29]
SF-12	Generic QoL instrument derived from SF-36; SF-12 consists of 12 items (from SF-36); scoring and weighting produces two summary scores: physical health (PCS) and mental	No	Unknown	May be of particular value in large studies for monitoring changes in physical

Instrument	Description	Validated in UI?	MCID	Comments
	health (MCS).[33,34]			and mental health outcomes.[47]
EQ-5D	Generic QoL instrument consisting of 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and 243 distinct health states. Each dimension has 3 possible levels: 1 = no problems, 2 = some problems, 3 = extreme problems. Weighted scoring produces EQ-5D index score. A 20 cm visual analog scale (EQ-VAS; range: 0 to 100) with anchors of "worst imaginable health state" (0) and "best imaginable health state"(100) is used by patient for rating health today by drawing a line from an anchor box to corresponding point on scale.[49,50]	Yes[53]	Unknown	Not certain whether EQ-5D adequately captures utility around incontinence indirectly through its existing dimensions.[53]

EQ-5D = European Quality of Life Five Dimensions Questionnaire; EQ-VAS = European Quality of Life Scale Visual Analogue Scale; I-QOL = Incontinence Quality of Life Questionnaire; KHQ = King's Health Questionnaire; MCID = minimal clinically important difference; MCS = mental component summary; OAB = overactive bladder; PCS = physical component summary; pts = points; QoL = quality of life; SF-36 = 36-Item Short-Form Health Survey; SF-12 = 12-Item Short-Form Health Survey; UI = urinary incontinence.

Conclusion

Of the four quality of life instruments — I-QOL, KHQ, SF-12, and EQ-5 — used in the included Ona A trials, all except the SF-12 were validated to some extent in urinary incontinence. A between-group MCID of 2.5 points was identified for total I-QOL score in patients with stress incontinence, while a within-group MCID of 5 points was identified for each domain of the KHQ in patients with OAB.

APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY

Objective

To summarize the results of study 191622-096,[54] the open-label extension study for patients completing either of the two phase 3 pivotal trials (study 191622-095[21] or 191622-520[20]). The following summary is based on unpublished data provided by the manufacturer.

Findings

Study Design

Patients completing either of two phase 3 pivotal trials (study 191622-095[21] or 191622-520;[20] total n = 1,106) were eligible to be enrolled in an open-label extension study (study 191622-096)[54] for up to 104 weeks following entry into this open-label extension study to evaluate the long-term safety and efficacy of onabotulinumtoxinA (Ona A). During the extension study, all patients fulfilling all treatment criteria (listed below) received active treatment with Ona A in doses of 100 units (if second treatment), or 150 units if they met the pre-defined criteria (listed below)). Post-treatment follow-up occurred at two, six, and 12 weeks; further follow-up occurred thereafter every 12 weeks until such time that further re-treatment was required or the patient exited the study.

For the patient to qualify for treatment, all of the following criteria had to be met: patient had to initiate the request for treatment; patient had to have experienced two or more urge-incontinence episodes, with no more than one urge incontinence–free day, as recorded in a three-day diary in the week prior to the qualification for the treatment 2 visit; a minimum of 12 weeks had to have elapsed since the previous treatment; patient had to have a post-void residual urine volume of < 200 mL; and the investigator had to have deemed treatment to be appropriate.

Patients received Ona A 150 units if they fulfilled the following criteria: it was at least their third treatment (i.e., treatment 1 and treatment 2 had already been received; the patient wanted an increase in study treatment and was willing to receive a higher dose; the patient's post-void residual urine volume was < 200 mL; and the investigator deemed treatment to be appropriate.

Results

At the time of the interim data cut-off (July 29, 2011), 834 patients had enrolled and 814 were included in the Ona A–treated population (i.e., enrolled into the long-term study and had had at least one dose of Ona A in either of the two phase 3 pivotal trials [095 or 520] or the open-label extension study [096]); no patients had completed the open-label extension study. Most patients (89.6% [729 out of 814]) were still ongoing, while 10.4% (85 out of 814) had discontinued the study. During the study, a majority of Ona A–treated patients had received the 100-unit (76.5% [623 out of 814]) compared with the 150-unit (23.5% [191 out of 814]) Ona A dose (Table 20). The total duration of Ona A exposure was defined as the number of days from the administration of the first Ona A treatment until the day of study exit or interim data cut-off. The median duration of Ona A exposure across treatment cycles was 45.8 weeks (range: 0.1 to 91.9 weeks) for all Ona A doses, and 43.1 weeks (range: 0.1 to 88.4 weeks) for the 100-unit dose.

TABLE 20: PATIENT DISPOSITION — ONA A–TREATED POPULATION

Disposition	Ona A 100 Units[a] (n = 623)	Ona A 150 Units[b] (n = 191)	All Ona A Doses (n = 814)
Enrolled	623	191	814
Completed, n (%)	0 (0)	0 (0)	0 (0)
Ongoing, n (%)	572 (91.8)	157 (82.2)	729 (89.6)
Discontinued, n (%)	51 (8.2)	34 (17.8)	85 (10.4)
Adverse event	6 (1.0)	5 (2.6)	11 (1.4)
Lack of efficacy	3 (0.5)	13 (6.8)	16 (2.0)
Pregnancy	0 (0)	0 (0)	0 (0)
Lost to follow-up	6 (1.0)	1 (0.5)	7 (0.9)
Personal reasons	24 (3.9)	9 (4.7)	33 (4.1)
Protocol violation	1 (0.2)	0 (0)	1 (0.1)
Other	11 (1.8)	6 (3.1)	17 (2.1)

Ona A = onabotulinumtoxinA.
[a] The 100 U Ona A group includes patients who received 100 U Ona A treatment(s) throughout the evaluation period.
[b] The 150 U Ona A group includes patients who received at least one dose of 150 U Ona A treatment (after receiving at least one dose of 100 U Ona A) during the evaluation period.

At baseline, Ona A–treated patients receiving the 100-unit dose during the extension trial had a mean (standard deviation [SD]) age of 60.4 (13.1) years, a mean (SD) overactive bladder (OAB) history of 6.5 (7.8) years, and were predominantly female (90.7%) and Caucasian (92.6%); 41.8% of patients were 65 years of age or older. At baseline, the 100 unit treatment subgroup experienced a mean (SD) of 5.4 (3.5) urinary incontinence, 4.9 (3.3) urinary urgency incontinence, 11.6 (3.4) micturition, 8.4 (4.0) urgency, and 2.1 (1.4) nocturia episodes per day. These baseline data generally tended to reflect the baseline data from the phase 3 pivotal trials, except for OAB history, which also appeared to differ between the two phase 3 trials.

The median time for an Ona A re-treatment request (i.e., time between treatment and request for subsequent treatment), regardless of Ona A dose, was 23.3 weeks for cycle 1, 24.0 weeks for cycle 2, and 16.6 weeks for cycle 3. Urinary-incontinence episodes, identified by the highest proportion of patients, comprised the most frequent OAB symptom driving requests for re-treatment. It is difficult to compare the consistency of the extension trial's efficacy findings with those of the two phase 3 trials because of the lack of placebo comparator in the extension trial. In addition, the extension trial permitted repeated administration of Ona A treatment, which was not a design feature of the phase 3 trials. Despite these limitations, directionally speaking, the patients receiving the 100 unit dose of Ona A appeared to show consistent decreases from the baseline data from the two phase 3 pivotal trials in micturition, urinary incontinence, nocturia, and urgency episodes over the subsequent treatment cycles for which data are available. Similarly, improvements were noted in the Incontinence Quality of Life Questionnaire (I-QOL) instrument and the King's Health Questionnaire (KHQ; i.e., role limitations and social limitations domains); however, the magnitude of improvement in I-QOL score appeared to decline over repeated cycles of treatment. The proportion of patients with ≥ 50% improvement in urinary-incontinence episodes also seemed to decline (67.9%, 64.5%, 55.0%, and 53.3%) over repeated cycles of treatment.

TABLE 21: NUMBER OF PATIENTS IN EACH ONA A TREATMENT CYCLE (ONA A–TREATED POPULATION)

Ona A Treatment Cycle	Ona A 100 Units[a]	Ona A 150 Units[a]	All Ona A Doses
Cycle 1	814	0	814
Cycle 2	452	94	546
Cycle 3	138	115	253
Cycle 4	33	55	88
Cycle 5	8	15	23
Cycle 6	2	2	4
Overall[b]	623	191	814

Ona A = onabotulinumtoxinA.
[a] The treatment group is based on the actual Ona A treatment that a patient received at each cycle.
[b] The 100-unit Ona A group includes patients who received 100 units Ona A treatment throughout the evaluation period, and the 150-unit Ona A group includes patients who received at least one dose of 150 units of Ona A treatment (after receiving at least one dose of 100 units Ona A) during the evaluation period.

Adverse events are presented in Table 22. Since these adverse events reflect the effect of repeated Ona A treatments, it is potentially problematic to draw comparisons between the adverse event data from the extension trial and those from the phase 3 trials. Nonetheless, at the end of cycle 1, the proportion of patients experiencing any adverse events seemed comparable with that reported for Ona A–treated patients in study 191622-095,[21] but higher than that reported for 191622-520.[20] Serious adverse events in the extension trial seemed to occur slightly more often than in either of the two phase 3 trials, while withdrawals due to adverse events appeared to be less frequent in the extension trial than the phase 3 trials (Table 22).

TABLE 22: ADVERSE EVENTS

	Ona A 100 Units			
Ona A Treatment Cycle	1 (n = 814)	2 (n = 452)	3 (n = 138)	4 (n = 33)
All AEs (%)	534 (65.6)	273 (60.4)	72 (52.2)	18 (54.5)
Deaths (%)	0	0	0	0
SAEs (%)	54 (6.6)	28 (6.2)	8 (5.8)	0 (0.0)
Discontinuations Due to AEs[a] (%)	2 (0.2)	4 (0.9)	1 (0.7)	0 (0.0)

AE = adverse event; Ona A = onabotulinumtoxinA; SAE = serious adverse event.
[a] All adverse events that started during treatment cycles 1, 2, 3, and 4 leading to discontinuation are included, regardless of relationship to treatment.

The frequency of urinary tract infections (UTIs) seemed stable across four cycles of Ona A treatment in the extension trial and comparable to the frequency of UTI reported in study 191622-520,[20] but higher than that reported for study 191622-095.[21] Urinary retention appeared to occur at a lower frequency in the extension trial compared with the phase 3 trials, and at a similar frequency across four cycles of Ona A treatment (Table 23).

TABLE 23: NUMBER OF PATIENTS WITH URINARY TRACT INFECTION AND URINARY RETENTION

	Ona A 100 Units			
Ona A Treatment Cycle	1 (n = 814)	2 (n = 452)	3 (n = 138)	4 (n = 33)
Urinary Tract Infection (%)	205 (25.2)	106 (23.5)	28 (20.3)	7 (21.2)
Urinary Retention (%)	33 (4.1)	17 (3.8)	5 (3.6)	1 (3.0)

Ona A = onabotulinumtoxinA.

Bladder and kidney ultrasound examinations were performed serially pre- and post-treatment and at study exit to detect the presence of kidney and bladder stones. There were no abnormal findings reported from bladder ultrasound. Renal cysts were said to be observed in the majority of cases, but the frequencies were not reported. Other findings by renal ultrasonography revealed the following in patients who received Ona A 100 units:

- Cycle 1: six patients with kidney stones and one patient with pyelocaliectasis
- Cycle 2: two patients with hydronephrosis, one patient with pyelocaliectasis, and one patient with renal cancer (judged unrelated to study treatment)
- Cycle 3: one patient with hydronephrosis
- Cycle 4: no abnormal findings reported.

Summary

The assessment of long-term efficacy and safety data from this extension trial is limited by the open-label, non-comparative design of the extension trial and the non-availability of a more current dataset for the extension trial. Bearing in mind these limitations, the extension trial efficacy data seem generally supportive of the phase 3 trial findings. Likewise, there do not appear to be any new safety signals from these extension trial data.

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